HYDROGEN LABELING OF SOME HETEROAROMATIC CARBON ACIDS

By

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A DISSERTATION PRESENTED TO THE GRADUATE COUNCIL OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

UNIVERSITY OF FLORIDA
1973

To my Father -

with respect, admiration
and love.

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Chairman: John A. Zoltewicz
Major Department: Chemistry

Rates of hydrogen-deuterium exchange in the alkyl group at the 4-position of 1,4-dimethylpyridinium iodide and 4-isopropyl-1-methylpyridinium iodide in buffered D_2O solutions at 75.0° ± 0.1° were obtained by the use of nmr spectroscopy in order to determine the effects of methyl groups on carbon acid acidity. Deprotonation was observed to take place by general base catalyzed reactions. An excellent Brønsted correlation (β = 0.75) was obtained for the deprotonation of each carbon acid using a series of structurally unrelated bases. Two methyl substituents were found to exert very little rate-retarding effect on the kinetic acidity. The largest reactivity ratio, found for deuteroxide ion catalysis, shows the methyl acid to be more acidic kinetically than the

isopropyl acid by a factor of 6.69. Other bases and reactivity ratios are: phenoxide (2.71), 4-aminopyridine (2.42), acetate ion (1.98), and imidazole (1.20). The small effect of the methyl substituents on the kinetic acidity is explained on the basis of a transition state almost planar in structure with substantial charge delocalization into the heterocyclic ring.

Attempts to measure the relative equilibrium acidity of the two molecules in liquid ammonia by nmr spectroscopy were unsuccessful due to the instability of the conjugate base of the 4-methyl acid. It was determined, however, that the 4-methyl acid cannot be substantially more acidic, thermodynamically, than the 4-isopropyl acid.

Rates of hydrogen-deuterium exchange at the 6-position of 1,3,6-trimethylpyridazinium iodide and 3,6-diisopropyl-1-methylpyridazinium iodide in buffered D_2O solutions at 75.0 ± 0.1° were briefly examined. The isopropyl carbon acid is substantially less acidic kinetically than the methyl acid. The large reactivity difference is believed to be the result of steric inhibition of resonance in the deprotonated form of the acid.

CHAPTER I

INTRODUCTION

Great interest has been shown in the acidity of weak carbon acids and many investigations have been conducted on the effect of structural changes on that acidity.[1,2,3]

A carbon acid is an organic compound which when treated with a suitable base, donates a proton to that base by the breaking of a carbon-hydrogen bond. Since most organic compounds contain carbon-hydrogen bonds, most compounds are potential carbon acids. The study of the effects on the acidity of a carbon acid is, therefore, a study of widespread significance.

The acidity of carbon acids has been studied from two different approaches; kinetic acidity, dealing with the rate of the proton transfer reaction and thermodynamic acidity, dealing with the position of the equilibrium between the acid and its conjugate base.

For weak carbon acids, the rates at which protons are transferred from carbon can be measured much more easily than equilibrium constants, the most commonly used method being base-catalyzed hydrogen isotope exchange. Using this technique, kinetic acidities of a wide variety of carbon acids have been studied including arenes, sulfides, sulfones, carbonyl compounds, halo and cyano compounds, and

nitroalkanes. Much of this work has involved attempts to elucidate the relationship between structural changes in a series of compounds with the effects of these changes on the rate of the proton transfer reaction. In the present study, the effects of methyl substituents on the acidity of some alkyl-substituted heteroaromatic carbon acids were investigated.

The effect of the methyl group on carbon acid acidity is an interesting subject since at first glance it might seem that its behavior is quite erratic. Methyl groups usually decrease both kinetic and equilibrium acidities of carbon acids. The retardation effect of one methyl group on the rate of proton transfer has been reported to be as high as 700.[4] It has also, however, been reported to be so low as to have practically no effect at all.[5,6] And in some systems, for example the nitroalkanes or fluorenes, a methyl substituent even acts to increase the carbon acid equilibrium acidity.

In order to determine the effect of methyl substituents on acidity in the 4-alkyl-1-methylpyridinium iodide system, hydrogen isotope exchange experiments were carried out with a number of different bases in buffered D_2O solutions and the rates of the second-order reactions were determined by nmr spectroscopy. The relative kinetic acidities of 1,4-dimethylpyridinium iodide and 4-isopropyl-1-methylpyridinium iodide were determined. The magnitude of the relative acidities of the two compounds is explained on the basis

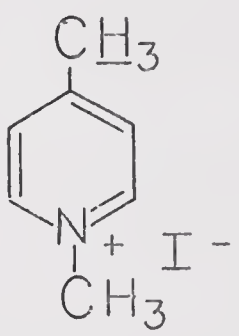
of the structure of the transition state of the proton transfer reaction. Attempts were also made to obtain information on the equilibrium acidities of these two molecules by studying their nmr spectra in liquid ammonia. The kinetic acidities of 1,3,6-trimethylpyridazinium iodide and 3,6-diisopropyl-1-methylpyridazinium iodide were also briefly examined.

CHAPTER 2

ALKYL GROUP HYDROGEN-DEUTERIUM EXCHANGE IN 4-ALKYL-1-METHYLPYRIDINIUM IODIDES

Results

The kinetics of H-D exchange in the 4-alkyl group, (exchangeable protons underlined), of 1,4-dimethylpyridinium iodide, I, 4-ethyl-1-methylpyridinium iodide, II, and 4-isopropyl-1-methylpyridinium iodide, III, in buffered D_2O solutions of 1.0 M ionic strength (KCl added) were compared at 75.0 ± 0.1°. The exchange reactions were followed by measuring the change in the integrated area of the appropriate nmr signals relative to that of a non-exchanging internal standard present in the reaction mixture. The standard chosen was either tetramethylammonium bromide or sodium acetate.



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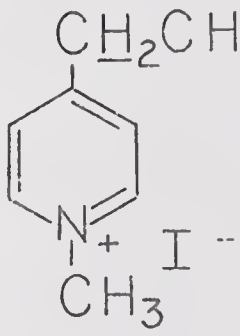

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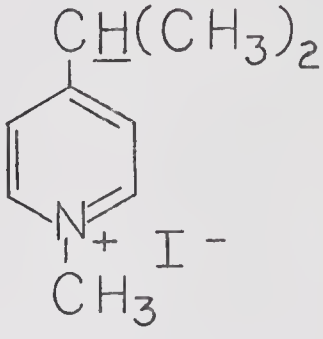


III

In the isotope exchange reactions of these compounds, deprotonation could take place by either or both of the

following pathways employing catalytic bases OD^- and B, Scheme 1.

Scheme 1

$$C\text{-}H + OD^- \rightleftharpoons C^- + HOD \xrightarrow{D_2O} C\text{-}D + OH^-$$

$$C\text{-}H + B \rightleftharpoons C^- + BH^+ \xrightarrow{D_2O} C\text{-}D + B$$

Since the reactions are carried out in D_2O, (110 M in D), and the substrate concentration is never more than 0.6 M, it is reasonable to assume that the concentrations of both HOD and BH^+ are small enough to make the exchange reaction effectively irreversible.

The rate of deprotonation, therefore, can be expressed by equation 1,

$$\text{rate} = k_{OD}[C\text{-}H][OD^-] + k_B[C\text{-}H][B] \qquad (1)$$

where k_{OD} is the second-order rate constant for deprotonation by OD^- ion and k_B is the second-order rate constant for deprotonation by buffer base.

The reactions were carried out in buffered D_2O solutions. Since base is not consumed, the concentrations of OD^- and B are constant and the reaction is pseudo-first-order, i.e., only the H content of the substrate changes with time. Therefore, equation 2 can be written for the pseudo-first-order rate constant associated with the deprotonation reaction.

$$k_{\psi} = k_{OD}[OD^{-}] + k_{B}[B] \qquad (2)$$

Preliminary Experiments

In order to approximate the reactivity differences between the three compounds I - III, they were studied by pairs in the same buffer solutions. First, both the 4-methyl compound, I, and the 4-ethyl compound, II, were dissolved in separate portions of the same 10:1 bicarbonate-carbonate buffer solution and heated at 75.0 ± 0.1°. Since both compounds were subjected to the same conditions, the assumption was made that a relative reactivity ratio could be obtained from the ratio of the respective reaction half-lives, the reactivity ratio being the inverse of the half-life ratio. Comparison of the compounds in this manner indicated the 4-methyl protons of compound I are 1.8 times more acidic than the methylene protons of the 4-ethyl group of compound II.

The 4-ethyl compound, II, was then compared to the 4-isopropyl compound, III, by means of a 2:3 bicarbonate-carbonate buffer solution at 75.0 ± 0.1° and comparison of the half-lives for these two exchange reactions indicated the methylene protons of the 4-ethyl compound, II, are more acidic than the methine proton of the 4-isopropyl compound, III, by a factor of 5.

Combining these two ratios, the relative acidities of the protons of the three different groups is obtained; methyl / ethyl / isopropyl is 9 / 5 / 1. It appears that the rate retarding effects of the methyl groups are

approximately additive, one methyl group decreasing the rate of deprotonation by a factor of about 4. Considering the relatively small reactivity difference between the methyl and isopropyl groups, it was decided to concentrate on these two compounds and discontinue further study of the 4-ethyl compound.

Deuteroxide Ion Catalysis

The value of k_ψ for H-D exchange in a 4-alkyl-1-methyl-pyridinium iodide is expected to be dependent, equation 2, on both the deuteroxide ion concentration and the buffer base concentration, i.e., the reaction is expected to be general base catalyzed. If the exchange proceeded by specific base catalysis, i.e., either no buffer base catalysis, $k_B=0$, or there were no buffer base present, $[B]=0$, the expression for the pseudo-first-order rate constant would simplify to equation 3

$$k_\psi = k_{OD}[OD^-] \qquad (3)$$

and a value for k_{OD} could easily be obtained by measurement of the observed rate and the pD of the solution.

For this purpose, a saturated $Ca(OD)_2$ solution was employed. This material has been shown to be an effective alkaline pH standard.[7] Due to its inclination to supersaturate at higher temperatures, however, it was necessary to carry out the reactions in solutions with a small amount of solid $Ca(OD)_2$ present to insure constant base concentration.

It was decided to obtain k_{OD} values not only at 75.0° but also at 25.0° and 50.0° so that values of the energies and entropies of activation for the 4-methyl and 4-isopropyl compounds could be calculated. On performing the kinetic runs, however, it was found that at 25.0°, the 4-isopropyl compound was too unreactive and at 75.0°, the 4-methyl compound reacted too rapidly. As a result, second-order rate constants could not be obtained in these two cases. The values that were obtained are listed in Table I.

Since it was not possible to obtain a value of k_{OD} for the 4-methyl compound in $Ca(OD)_2$ at 75.0°, it was necessary to try a less basic buffer and apply equation 3 to obtain a value for k_{OD} and also a value for k_B, the buffer base catalysis constant.

A phenol buffer was chosen and several runs were carried out on both the 4-methyl and the 4-isopropyl compounds using different buffer concentrations and ratios. In order to obtain values for k_{OD} and k_B, equation 2 was rearranged to the standard form of an equation defining a straight line, equation 4.

$$\frac{k_\psi}{[OD^-]} = k_B \frac{[B]}{[OD^-]} + k_{OD} \qquad (4)$$

Use of this equation to obtain values for k_{OD} and k_B required the construction of a graph with axes of $k_\psi/[OD^-]$ and $[B]/[OD^-]$. Determination of the slope of the line obtained by plotting these two quantities provided the value of k_B. The values obtained, $1.27 \times 10^{-2} M^{-1} sec^{-1}$

Table 1. Rate Constants for H-D Exchange of 1,4-Dimethyl- and 4-Isopropyl-1-methylpyridinium Iodides by Deuteroxide Ion.

Buffer	T, °C	k_{OD}, M^{-1} sec^{-1} 4-Methyl	k_{OD}, M^{-1} sec^{-1} 4-Isopropyl
Calcium Deuteroxide	25.0	8.68×10^{-3}	---
	50.0	7.30×10^{-2}	7.78×10^{-3}
	75.0	---	6.55×10^{-2}
Phenol	75.0	4.00×10^{-1}	6.5×10^{-2}
4-Amino-2,6-Dimethyl-pyridine	75.0	4.75×10^{-1}	---

for the methyl compound and $4.68 \times 10^{-3}\ M^{-1}\ sec^{-1}$ for the isopropyl compound, indicate the methyl compound to be more reactive toward phenoxide ion by a factor of 2.7. The intercept provided the value for k_{OD}. The values obtained, $4.00 \times 10^{-1}\ M^{-1}\ sec^{-1}$ for the methyl compound and $6.5 \times 10^{-2}\ M^{-1}\ sec^{-1}$ for the isopropyl compound, indicate the methyl compound to be more reactive toward deuteroxide ion by a factor of 6.15.

It should be noted that considerable difficulty was encountered in obtaining a consistent value for the experimental pKa of phenol from the relationship pKa = pD + $\log[BD^+]/[B]$ when this was applied to reaction mixtures containing the buffer. Close examination of this problem led to the conclusion that the source of the error was in the pD measurement.

The high concentration of iodide ion together with silver ion from the electrode electrolyte solution slowly clogged the porous electrode reference junction causing substantial drifts in pD measurements. Elimination of this drift was accomplished by the use of a thiosulfate wash of the electrode but deviations of the pKa values could not be eliminated, due possibly to interaction between substrate and phenol buffer. As a consequence, it was necessary, for this one buffer, to determine a pKa in the absence of substrate and to use this value to calculate hydrolysis corrections and pD values in the manner now outlined.

Any buffer can undergo hydrolysis reactions which serve to change the initial buffer ratio. A buffer acid can dissociate into D^+ and its conjugate base and, similarly, buffer base can react with D_2O to generate its conjugate acid and OD^-. The extent of such reactions for a particular buffer is determined by the solution acidity and the buffer concentration. For alkaline solutions, a measure of the extent of hydrolysis is given by the concentration of OD^-. This concentration may, therefore, be used to correct initial concentrations for hydrolysis.

In order to calculate hydrolysis corrections, equations 5 and 6,

$$[D^+][OD^-] = K_{D_2O} \tag{5}$$

$$\frac{[D^+][B]}{[BD^+]} = K_a \tag{6}$$

where [B] and $[BD^+]$ are the equilibrium concentrations of buffer base (phenoxide ion) and conjugate acid (phenol) respectively, were combined to give equation 7.

$$K_a/K_{D_2O} = \frac{[B]}{[OD^-][BD^+]} \tag{7}$$

Equilibrium concentrations of B and BD^+ are obtained from equations 8 and 9

$$[B] = [B]_0 - [OD^-] \tag{8}$$

$$[BD^+] = [BD^+]_0 + [OD^-] \tag{9}$$

where $[B]_0$ and $[BD^+]_0$ are the initial concentrations of buffer base and conjugate acid, respectively.

Substitution into equation 7 of the experimentally determined equilibrium constant, of a calculated value for K_{D_2O} at 75°,[8,9] and of equivalent quantities of [B] and $[BD^+]$ as given by equations 8 and 9 results in equation 10.

$$\frac{1.26 \times 10^{-10}}{2.98 \times 10^{-14}} = \frac{[B]_0 - [OD^-]}{[OD^-]([BD^+]_0 + [OD^-])} \qquad (10)$$

Equation 10 has the form of a quadratic equation (11) where

$$ax^2 + (ab + 1)\,x - c = 0 \qquad (11)$$

$a = \frac{1.26 \times 10^{-10}}{2.98 \times 10^{-14}}$, $b = [BD^+]_0$, $c = [B]_0$, and $x = [OD^-]$.

This equation was used to obtain $[OD^-]$ directly. This value, when applied to equations 8 and 9, gave the equilibrium concentrations of the species B and BD^+. In all cases, the correction for [B] was less than 5 percent. Of the eleven corrections for $[BD^+]$ involving both the methyl and isopropyl compounds, the correction in all but three cases was also less than 5 percent. Of the three remaining cases, two corrections of 13 percent were made, one for each compound. In one case involving the 4-isopropyl compound under the most basic conditions employed, a correction to $[BD^+]_0$ of 50 percent was necessary.

Buffer concentrations and kinetic results for the two compounds in phenol buffer are reported in Tables 2 and 3.

Table 2. Kinetic Data for H-D Exchange of 1,4-Dimethylpyridinium Iodide in Phenol Buffers at 75.0°.[a]

k_ψ, sec^{-1}	pD[b]	[B], M[b]	$[BD^+]$, M[b]	$[B]/[OD^-]$	$k_\psi/OD^-]$, $M^{-1}sec^{-1}$
2.665×10^{-4}	9.125	1.92×10^{-2}	1.85×10^{-1}	4.84×10^{2}	6.71
1.373×10^{-4}	9.125	9.56×10^{-3}	9.25×10^{-2}	2.41×10^{2}	3.47
2.448×10^{-5}	8.903	1.90×10^{-3}	1.85×10^{-2}	7.98×10^{2}	1.03
3.600×10^{-4}	10.276	1.04×10^{-2}	4.35×10^{-3}	1.85×10^{1}	6.41×10^{-1}
3.830×10^{-5}	8.903	1.85×10^{-3}	1.84×10^{-2}	7.77×10^{1}	1.62

[a] pKa = 9.90.

[b] Calculated values, see text.

Table 3. Kinetic Data for H-D Exchange of 4-Isopropyl-1-methylpyridinium Iodide in Phenol Buffers at 75.0°.[a]

k_ψ, sec^{-1}	pD[b]	[B], M[b]	$[BD^+]$, M[b]	$[B]/[OD^-]$	$k_\psi/[OD^-]$, $M^{-1}sec^{-1}$
9.505×10^{-5}	9.125	1.92×10^{-2}	8.29×10^{-2}	4.84×10^{2}	2.39
1.880×10^{-4}	9.643	3.82×10^{-2}	7.08×10^{-2}	2.92×10^{2}	1.43
3.827×10^{-5}	9.125	7.62×10^{-3}	4.69×10^{-2}	1.92×10^{2}	9.64×10^{-1}
1.642×10^{-4}	10.166	2.83×10^{-2}	1.53×10^{-2}	6.48×10^{1}	3.77×10^{-1}
4.303×10^{-4}	10.927	5.50×10^{-2}	4.97×10^{-3}	2.18×10^{1}	1.71×10^{-1}
8.368×10^{-5}	10.276	1.04×10^{-2}	4.35×10^{-3}	1.85×10^{1}	1.49×10^{-1}

[a] pKa = 9.90.

[b] Calculated values, see text.

Graphical treatment of the data in the manner previously described gave the results shown in Figures 1 and 2.

Comparison of the value of k_{OD} for the 4-isopropyl compound obtained from the phenol buffer runs (6.5×10^{-2} $M^{-1}sec^{-1}$) with the value obtained from $Ca(OD)_2$ solution ($6.55 \times 10^{-2} M^{-1} sec^{-1}$) shows a more than satisfactory agreement. Since only one determination of the value of k_{OD} for the 4-methyl compound has been obtained, however, it would be appropriate to use another buffer to verify the value of $4.00 \times 10^{-1} M^{-1} sec^{-1}$ derived from the phenol buffer runs.

For this purpose, 4-amino-2,6-dimethylpyridine was chosen as a buffer. Buffer solutions of this compound are not as basic as the phenol buffer solutions but the two methyl groups ortho to the pyridine nitrogen would be expected to favor reaction by deuteroxide ion by sterically hindering reaction by the buffer base.

Four rates were measured using the 4-amino-2,6-dimethylpyridine buffer. The conditions employed and results obtained can be found in Table 4. Graphical treatment of the results in a manner similar to that used for the phenol buffer runs is shown in Figure 3.

The value of k_{OD} obtained for the 4-methyl compound using the pyridine buffer is also included in Table 1. This value, $4.75 \times 10^{-1} M^{-1} sec^{-1}$, and the value obtained using the phenol buffer, $4.00 \times 10^{-1} M^{-1} sec^{-1}$, were then

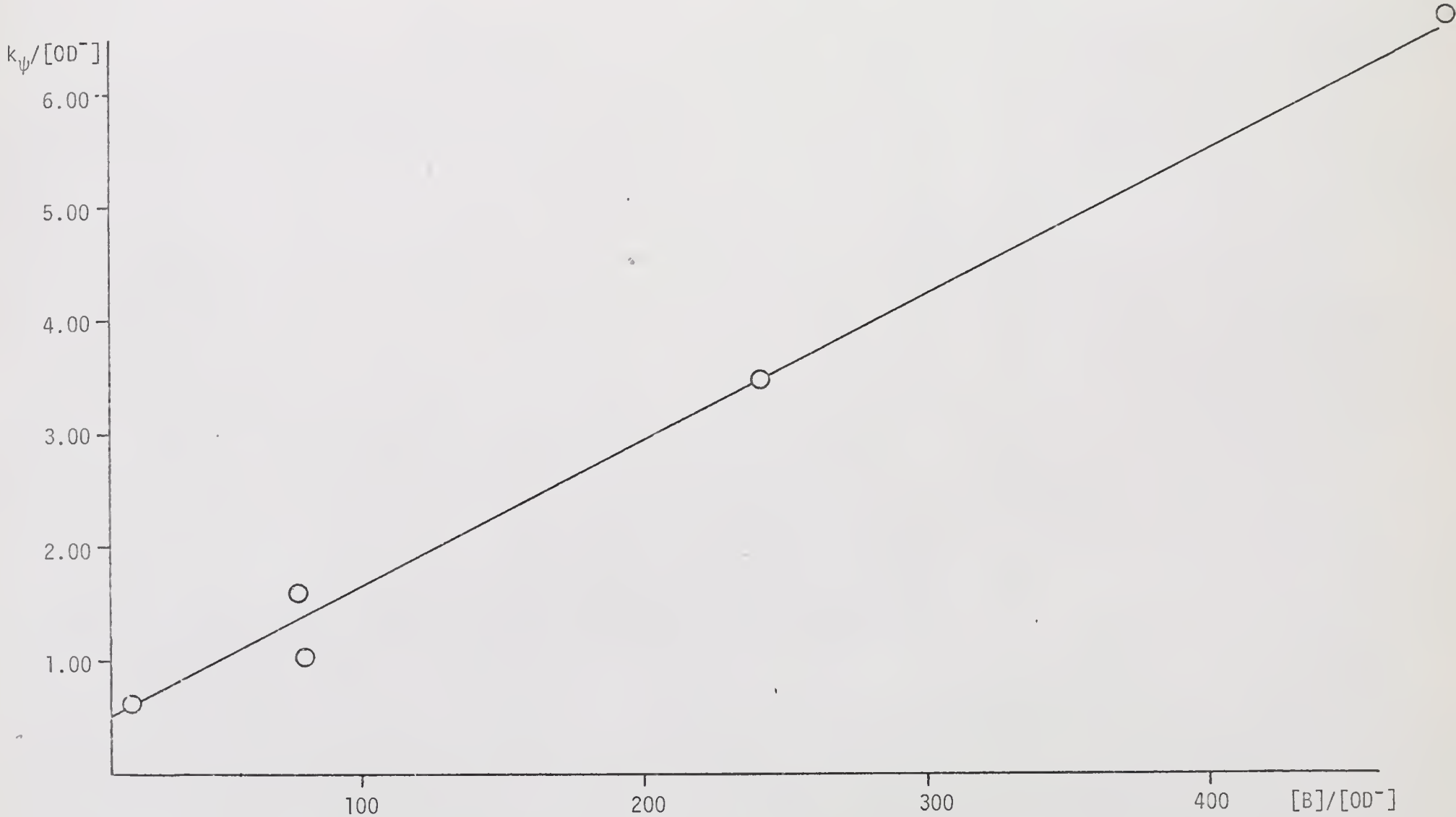


Figure 1. Plot of Kinetic Data for H-D Exchange of 1,4-Dimethylpyridinium Iodide in Phenol Buffers at 75.0°. The slope, k_B, has the value $1.27 \times 10^{-1} M^{-1} sec^{-1}$, and the intercept, k_{OD}, is $4.00 \times 10^{-1} M^{-1} sec^{-1}$.

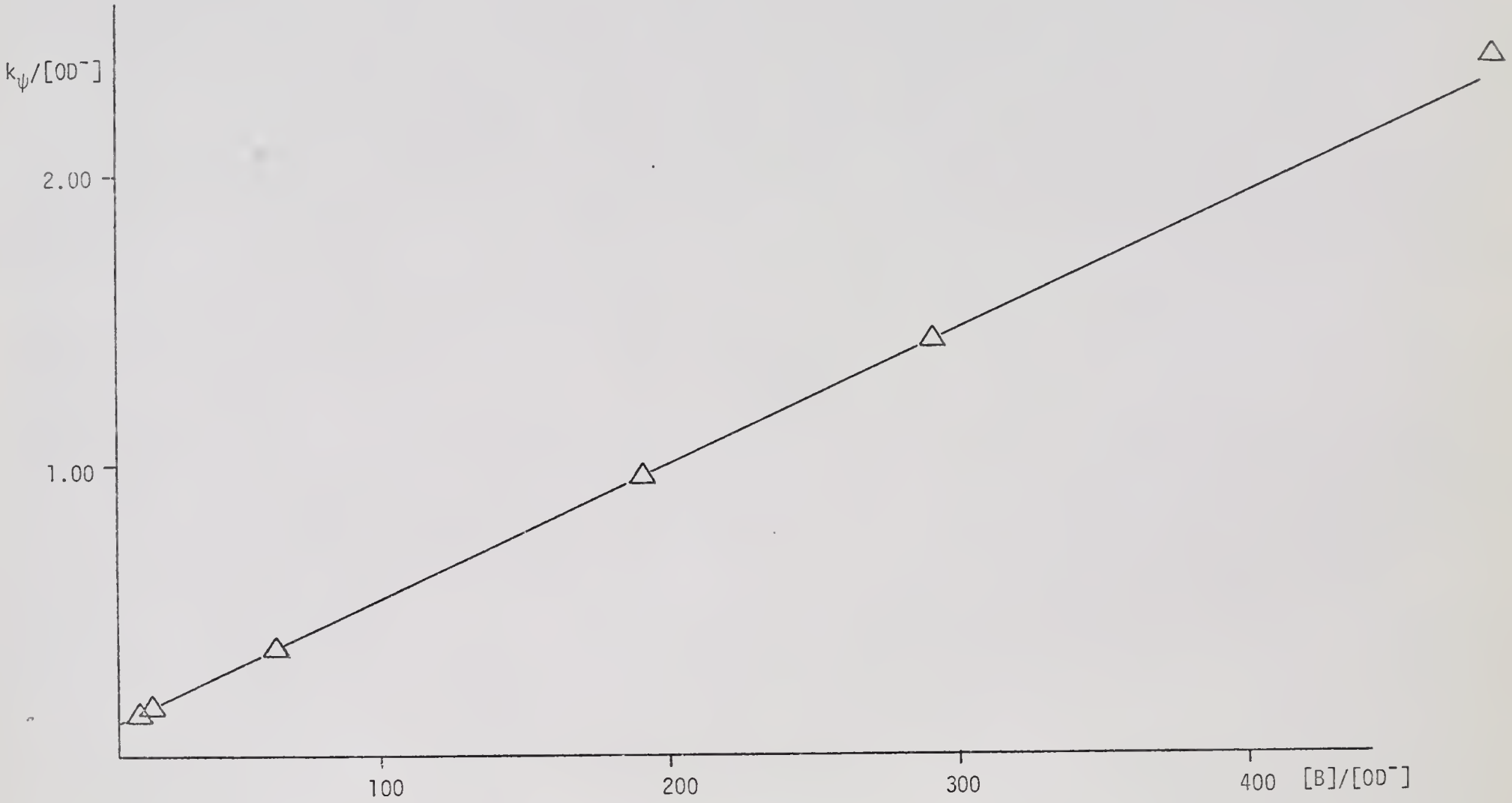


Figure 2. Plot of Kinetic Data for H-D Exchange of 4-Isopropyl-1-methylpyridinium Iodide in Phenol Buffers at 75.0°. The slope, k_B, has the value 4.68 x $10^{-3} M^{-1} sec^{-1}$ and the intercept, k_{OD}, is 6.5 x $10^{-2} M^{-1} sec^{-1}$.

Table 4. Kinetic Data for H-D Exchange of 1,4-Dimethylpyridinium Iodide in 4-Amino-2,6-dimethylpyridine Buffers at 75.0°.[a]

k_ψ, sec^{-1}	pD	[B], M	$[BD^+]$, M	$[B]/[OD^-]$	$k_\psi/[OD^-]$, $M^{-1}sec^{-1}$
7.423×10^{-5}	9.428	4.69×10^{-2}	5.53×10^{-2}	6.01×10^{2}	9.52×10^{-1}
1.068×10^{-4}	9.626	5.87×10^{-2}	4.35×10^{-2}	4.66×10^{2}	8.48×10^{-1}
3.097×10^{-5}	9.114	1.49×10^{-2}	3.62×10^{-2}	3.85×10^{2}	8.00×10^{-1}
5.205×10^{-4}	10.496	9.89×10^{-2}	9.98×10^{-3}	1.06×10^{2}	5.58×10^{-1}

[a] pKa = 9.50.

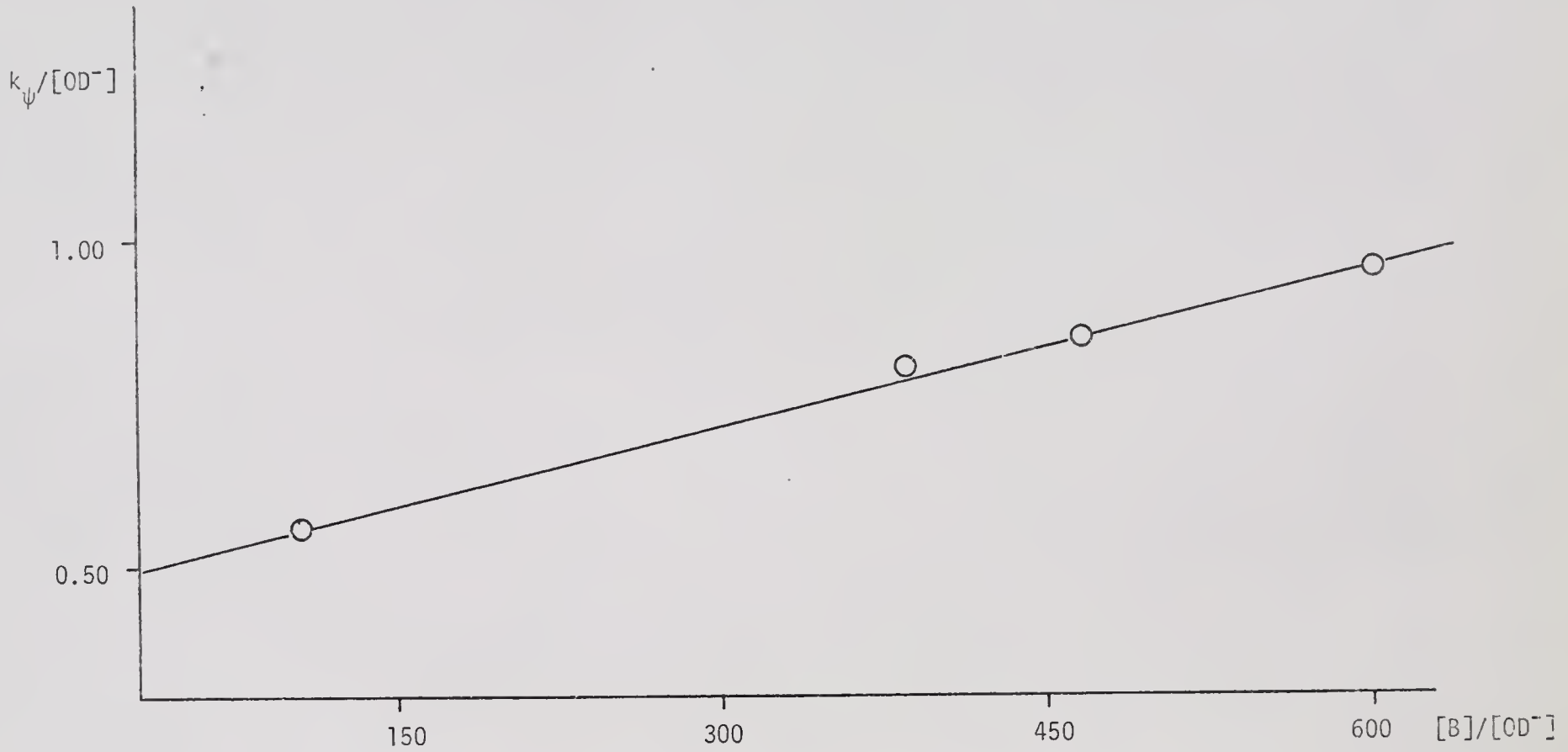


Figure 3. Plot of Kinetic Data for H-D Exchange of 1,4-Dimethylpyridinium Iodide in 4-Amino-2,6-Dimethylpyridine Buffers at 75.0°. The slope, k_B, has the value $8.05 \times 10^{-4} M^{-1} sec^{-1}$ and the intercept, k_{OD}, is $4.75 \times 10^{-1} M^{-1} sec^{-1}$.

averaged. Deviation of the two values from the average of $4.38 \times 10^{-1}\ M^{-1}\ sec^{-1}$ is less than 9 percent.

As a check on the values of k_{OD} obtained at the three temperatures, an Arrhenius plot of log k_{OD} versus the inverse of the temperature was constructed using the values of k_{OD} obtained in $Ca(OD)_2$ solution and, for the 4-methyl compound, the average of the two values obtained at 75.0° from buffer studies. The linearity of this plot, Figure 4, strongly suggests that the deuteroxide ion catalytic constants have been determined correctly.

Energies of activation and entropies of activation for the two compounds were calculated by equations 12 and 13.[10]

$$\log k_2 - \log k_1 = \frac{(E/2.303R)(T_2-T_1)}{T_2-T_1} \qquad (12)$$

$$\Delta S^{\ddagger}/2.303R = \log k - 10.753 - \log T + \left(\frac{E}{2.303RT}\right) \qquad (13)$$

Results are reported in Table 5. Pearson and Dillon[11] have compiled a list of activation energies and entropies for slow proton transfers from β-diketones and nitroalkanes. In comparison with those results it can be concluded that the deuteroxide ion catalyzed deprotonation of the two pyridinium iodides shows typical behavior for slow proton removal from weakly acidic species.

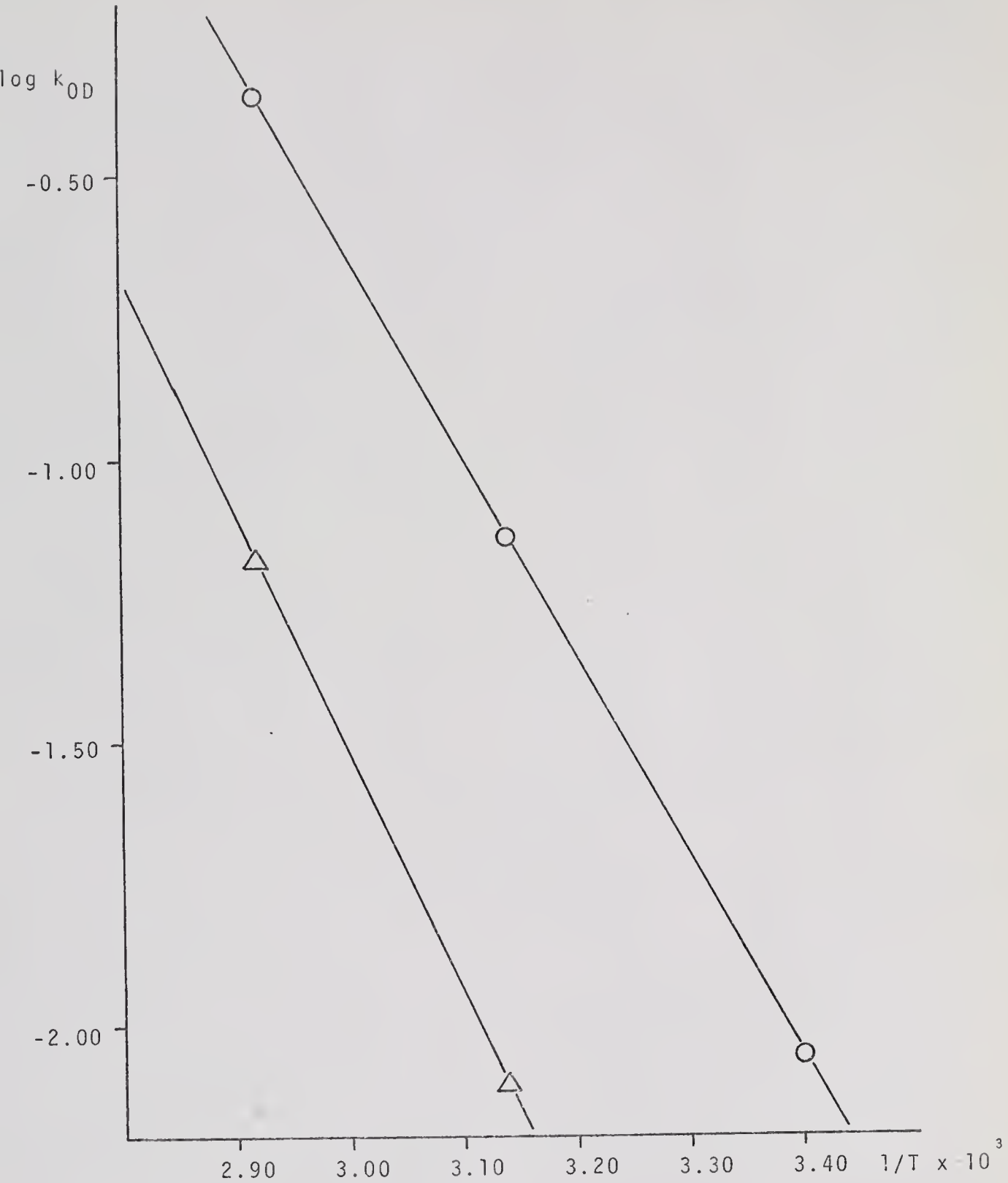


Figure 4. Arrhenius Plot of log k_{OD} versus 1/T for H-D Exchange of 1,4-Dimethyl(○)- and 4-Isopropyl (△)-1-methylpyridinium Iodides.

Table 5. Thermodynamic Constants for 1,4-Dimethyl- and 4-Isopropyl-1-methylpyridinium Iodides Reacting with Deuteroxide Ion.

	4-Methyl	4-Isopropyl
$E_{act.}$	16.3 kcal/mol.	19.2 kcal/mol.
$\Delta S^{\neq}$ [a]	-15.4 e.u.	-11.1 e.u.

[a] Calculated at 50.0°.

Catalysis by Other Buffers

With the value of k_{OD} known, k_B can be easily calculated for any buffer base once the pD is measured and k_ψ is obtained for any given kinetic run.

Rates were measured using six different buffers: 2,2,2-trifluoroethanol, 4-aminopyridine, imidazole, 2,6-dimethylpyridine, pyridine, and acetic acid. Buffer concentrations and kinetic results are given in Tables 6 and 7.

In the cases of four of these buffers (2,2,2-trifluoroethanol, 4-aminopyridine, imidazole, and acetic acid), kinetic runs were carried out as competition experiments. Both the 4-methyl and the 4-isopropyl compounds were run in the same solution. In this way, both the rate of reaction and the relative reactivity of the two compounds could be measured without regard to differences or changes in individual solutions.

In the cases of 2,6-dimethylpyridine and pyridine buffers only one of the substrates was used. It was not possible to study the 4-methyl compound in a 2,6-dimethylpyridine buffer due to methyl group overlap in the nmr spectrum. The 4-isopropyl compound was not studied in a pyridine buffer due to the lack of a suitable internal standard for nmr analysis. Exchange catalyzed by acetate ion, the usual internal standard employed in runs with the 4-isopropyl compound, is too competitive with exchange catalyzed by pyridine to allow reliable rate measurement.

Table 6. Kinetic Data for H-D Exchange of 1,4-Dimethyl-

Buffer	k_{ψ}, sec^{-1} [a]	pD	[B], M
2,2,2-Trifluoroethanol	5.488×10^{-4} [b]	9.918	1.59×10^{-3}
4-Aminopyridine	1.364×10^{-4} [c]	9.462	2.01×10^{-2}
	1.357×10^{-4} [c]	9.420	1.81×10^{-2}
Imidazole	6.462×10^{-6} [b]	7.731	2.09×10^{-1}
	2.500×10^{-6} [c]	6.646	1.00×10^{-1}
Pyridine	9.627×10^{-7}	6.447	1.87×10^{-1}
Acetic Acid	7.063×10^{-7}	6.271	2.01×10^{-1}

[a] Uncorrected for deuteroxide ion catalysis and acetate ion

[b] [acetate] = 0.100 M.

[c] [acetate] = 0.090 M.

[d] $pKa = pD + \log [BD^{+}]/[B]$.

pyridinium Iodide in Selected Buffers at 75.0°.

$[BD^+]$,M	$[OD^-]/[B]$	pKa,obsd[d]	k_B,$M^{-1}sec^{-1}$
1.71×10^{-2}	1.55×10^{-1}	10.95	2.78×10^{-1}
1.90×10^{-2}	4.29×10^{-4}	8.44	5.40×10^{-4}
1.90×10^{-2}	4.33×10^{-4}	8.44	5.60×10^{-4}
1.94×10^{-2}	7.67×10^{-6}	6.70	2.60×10^{-5}
1.00×10^{-1}	1.32×10^{-6}	6.65	2.15×10^{-5}
1.94×10^{-2}	4.47×10^{-7}	5.46	4.97×10^{-6}
1.91×10^{-2}	2.77×10^{-7}	5.25	3.39×10^{-6}

catalysis when present.

Table 7. Kinetic Data for H-D Exchange of 4-Isopropyl-1-

Buffer	k_{ψ}, sec^{-1} [a]	pD	[B], M
2,2,2-Trifluoroethanol	7.098×10^{-5} [b]	10.154	1.39×10^{-3}
	6.548×10^{-5} [c]	9.918	1.59×10^{-3}
4-Aminopyridine	4.810×10^{-5} [b]	9.462	2.01×10^{-1}
	4.907×10^{-5} [b]	9.420	1.81×10^{-1}
Imidazole	4.882×10^{-6} [c]	7.731	2.09×10^{-1}
	1.88×10^{-6} [b]	6.646	1.00×10^{-1}
2,6-Dimethylpyridine	3.19×10^{-8}	6.494	1.00×10^{-1}
Acetic Acid	3.505×10^{-7}	6.271	2.01×10^{-1}

[a] Uncorrected for deuteroxide ion catalysis and acetate ion

[b] [acetate] = 0.090 M.

[c] [acetate] = 0.100 M.

[d] $pKa = pD + \log [BD^{+}]/[B]$.

methylpyridinium Iodide in Selected Buffers at 75.0°.

$[BD^+]$,M	$[OD^-]/[B]$	pKa,obsd[d]	k_B,$M^{-1}sec^{-1}$
8.98×10^{-3}	3.06×10^{-1}	10.96	2.97×10^{-2}
1.71×10^{-2}	1.55×10^{-1}	10.95	3.08×10^{-2}
1.90×10^{-2}	4.29×10^{-4}	8.44	2.10×10^{-4}
1.90×10^{-2}	4.33×10^{-4}	8.44	2.42×10^{-4}
1.94×10^{-2}	7.67×10^{-6}	6.70	2.20×10^{-5}
1.00×10^{-1}	1.32×10^{-6}	6.65	1.72×10^{-5}
1.02×10^{-1}	9.29×10^{-7}	6.50	2.58×10^{-7}
1.91×10^{-2}	2.77×10^{-7}	5.25	1.72×10^{-6}

catalysis when present.

Also, use of the ring protons of the 4-isopropyl compound as a standard is prohibited by overlap of the pyridine ring protons in the nmr spectrum of mixtures of the two substances.

Attempts were made to obtain rate constants for D_2O acting as a base by use of 0.1 M DCl solutions but they proved unsuccessful. Both compounds appeared to degrade in the acidic solution. The methyl compound degraded approximately 10 percent after one week of heating; the isopropyl compound degraded about 10 percent after two weeks of heating. No exchange, as evidenced by the broadening of the 4-methyl singlet or the emerging of a singlet between the 4-isopropyl gem.-dimethyl doublet, could be detected in the nmr during this period.

Average values of the rate constants obtained in all buffers used along with the respective buffer pKa values are listed in Table 8. They are graphically represented by the Brønsted plot found in Figure 5. The equilibrium constants for D_2O and imidazole are statistically corrected to reflect the two acidic centers in each acid, i.e., pKa + log 2 values are used. Both the equilibrium constant and the rate constant for acetic acid are statistically corrected to reflect the two basic centers of the acetate ion, i.e., pKa - log 2 and log k_D - log 2 values are used.

Proteo control runs were carried out to verify the stability of the two pyridinium iodides in selected

Table 8. Summary of Rate Constants and pKa Values for 1,4-Dimethyl- and 4-Isopropyl-1-methylpyridinium Iodides Reacting in Selected Buffers at 75.0°.[a]

			4-Methyl		4-Isopropyl		
	Buffer	pKa	$k_2, M^{-1} sec^{-1}$	log k_2	$k_2, M^{-1} sec^{-1}$	log k_2	k_{rel}[c]
1	D_2O	15.54	4.38×10^{-1}	-0.36	6.55×10^{-2}	-1.18	6.69
2	CF_3CH_2OD[b]	10.95	2.78×10^{-1}	-0.56	3.03×10^{-2}	-1.52	---
3	Phenol	9.90	1.27×10^{-2}	-1.90	4.68×10^{-3}	-2.33	2.71
4	4-Amino-2,6-dimethyl-pyridine	9.50	8.05×10^{-4}	-3.09	---	---	---
5	4-Aminopyridine	8.44	5.50×10^{-4}	-3.26	2.27×10^{-4}	-3.64	2.42
6	Imidazole	6.98	2.37×10^{-5}	-4.63	1.97×10^{-5}	-4.71	1.20
7	2,6-Dimethylpyridine	6.50	---	---	2.58×10^{-7}	-6.59	---
8	Pyridine	5.46	4.97×10^{-6}	-5.30	---	---	---
9	Acetic Acid	4.95	1.70×10^{-6}	-5.77	8.60×10^{-7}	-6.07	1.98

[a] pKa and k_2 values are statistically corrected for the number of acidic and basic centers in the buffer.

[b] Values reported are uncertain. See text.

[c] $k_{rel} = k_{methyl} / k_{isopropyl}$.

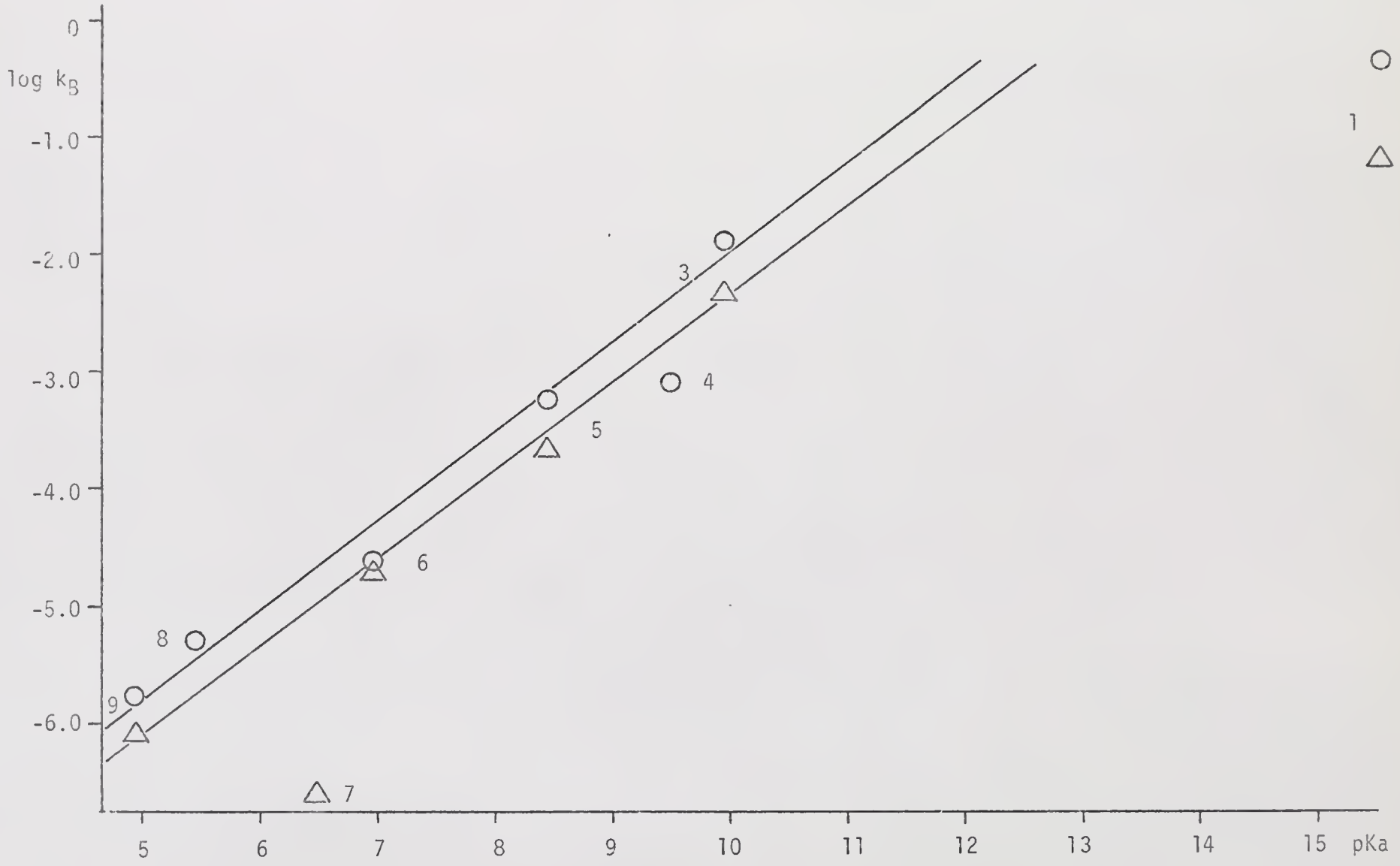


Figure 5. Brønsted Plot of log k_B versus pKa for 4-Methyl (○)- and 4-Isopropyl (△)-1-methylpyridinium Iodides in Selected Buffers at 75.0°.

buffers. The control runs on the 2,2,2-trifluoroethanol buffer showed substantial pH changes and new nmr peaks on heating. As a result, the values reported in Table 8 for this buffer are considered uncertain and are excluded from the Brønsted plot in Figure 5. Details of all the control runs are given in the experimental section.

The least squares lines calculated from the data in the Brønsted plot of Figure 5 give equation 14 for the 4-methyl compound and equation 15 for the 4-isopropyl compound. The uncertainty is expressed in terms of the standard deviation. The correlation coefficient (r) is also given. The Brønsted slopes are the same for

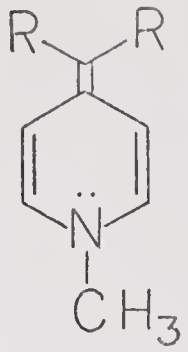
$$\log k_2 = (0.76 \pm .12)\ pKa - 9.62 \pm 0.96 \qquad r = .991. \qquad (14)$$

$$\log k_2 = (0.75 \pm .07)\ pKa - 9.86 \pm 0.58 \qquad r = .998 \qquad (15)$$

the two compounds.

NMR Spectra of 4-Alkyl-1-methylpyridinium Iodides in Liquid Ammonia

In order to obtain some knowledge of the equilibrium acidities of both 1,4-dimethyl- and 4-isopropyl-1-methylpyridinium iodides, nmr spectra of the two compounds in liquid NH_3 were recorded. It was hoped that observable amounts of the conjugate bases of the two compounds (IVa and IVb) would form. If so, the amount of the conversion could be used to provide some measure of the relative acidity of the two carbon acids in the basic solvent.



IV

a, R=H
b, R=CH_3

The compounds were added to nmr tubes along with about one milliliter of liquid NH_3. The tubes were then sealed, warmed to room temperature, and their nmr spectra recorded.

A solution of the 4-methyl compound in ammonia was opaque and dark green. The nmr spectrum, however, showed the presence of nothing other than the 4-methyl pyridinium iodide. Standing overnight resulted in no change in the spectrum although the formation of some solid precipitate in the tube was noted.

A solution of the 4-isopropyl compound was a clear orange. The nmr spectrum indicated that signals of the starting material and additional upfield signals attributable to the conjugate base were present. Integration showed approximately 10 percent of the pyridinium iodide had been converted to the conjugate base.

Ammonia solutions of the two compounds were prepared again and this time solid KOH was also added before the tubes were sealed.

The nmr spectrum of the opaque, dark green solution of the 4-methyl compound in ammonia with KOH added at -35° showed approximately 20 percent of the material had been converted to the conjugate base. Upon warming the solution to room temperature, the amount of this form increased so as to become the predominate form. However, the conjugate base apparently is unstable; signal strength slowly decreased until all nmr signals disappeared.

The nmr spectrum of the clear orange solution of the 4-isopropyl compound in ammonia with KOH added at -35° showed approximately 30 percent of the material had been converted to its conjugate base. Upon warming to room temperature, the only signals observed were those corresponding to the deprotonated form. After standing overnight, the spectrum was unchanged with no loss of signal.

Solutions of the pyridinium iodides in ammonia were then prepared with a benzene internal standard so that nmr chemical shifts could be assigned. Periodic integration of the 4-methyl solution indicated a 10 percent loss of substrate signal within an hour and a 20 percent loss after standing overnight.

The nmr assignments are reported in Table 9. Deprotonation of each carbon acid results in up-field shifts for the ring protons of the conjugate base. It is assumed that H-2,6 is at lower field than H-3,5 in the conjugate base, the same order as in the acid.[12]

Table 9. NMR Spectra of 1,4-Dimethyl- and 4-Isopropyl-1-methylpyridinium Iodides and Their Conjugate Bases in Ammonia.[a]

	1,4-Dimethyl		4-Isopropyl-1-methyl	
	Acid	Base	Acid	Base
CH_3	7.32	c	8.70[b]	8.45
CH	--	--	6.73[b]	--
NCH_3	5.43	c	5.42	7.07
H-3,5	1.92	4.45	1.87	4.63
H-2,6	0.80	3.78	0.70	3.98

[a] τ values with benzene, τ = 2.60, as internal standard.

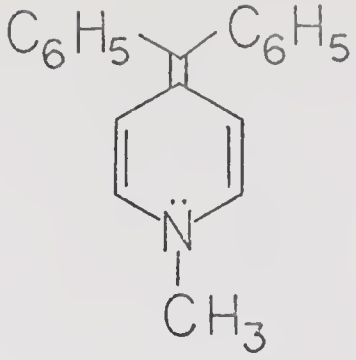
[b] J = 7 Hz.

[c] Presence of several peaks at high field precludes assignments.

It might at first appear that the 4-isopropyl compound is the more acidic of the two iodides in ammonia. However, due to the instability of the conjugate base of the 1-4-dimethylpyridinium ion, it cannot be conclusively stated that this is in fact the case. Nevertheless, on the basis of the results obtained, it can be stated that if the 4-methyl compound is the more acidic of the two carbon acids, the relative acidity ratio will be small.

Due to possible variation in the amount of KOD in solution, the amount of water present, and other possible complicating factors, the equilibrium acidities of the two compounds can only be properly compared by having both compounds in the same tube. As can be seen from the chemical shifts listed in Table 9, however, signal overlap makes this impossible.

It has previously been shown that the conjugate base of 1,4-dimethylpyridinium ion is unstable.[13] Ethereal solutions of the material, obtained by quickly extracting highly alkaline solutions of the pyridinium ion, rapidly degrade. Substitution in the alkyl group of electron withdrawing substituents, however, greatly enhances stability. For example, the conjugate base of 4-(α,α-diphenylmethyl)-1-methylpyridinium ion is a stable solid.[14]



Discussion

The Brønsted Correlation

The Brønsted plot in Figure 5, derived from the bases numbered 3, 5, 6, 8, and 9, shows remarkable correlation considering the different types of bases involved. Phenoxide ion, 3, two pyridines, 5 and 8, acetate ion, 9, and imidazole, 6, all fit the derived Brønsted line without significant deviation.

Behavior such as this is not unique in a Brønsted relationship. Strictly speaking, the Brønsted equation is expected to hold for a series of related bases with no significant structural or electronic differences such as a series of carboxylate anions or a series of structurally similar amines. Good correlations can be found, however, for bases of different types in some instances.

For example, the base-catalyzed H-D exchange of isobutyraldehyde-2-d has been studied extensively. Although the results for different classes of amines could not be

represented by a single Brønsted line,[15] both pyridine and phenoxide ion bases can be included in the same Brønsted relationship.[16]

As a better example, in a study of the base-catalyzed enolization of acetone, a reaction which like H-D exchange involves the removal of a proton as the rate determining step, it was found[17] that pyridines, carboxylate anions, and amines all fit a common Brønsted plot.

As previously stated, the correlation of the different types of bases in the Brønsted plot of Figure 5 is quite good. Mention should also be made, however, of those bases whose corresponding points do not fit the Brønsted relationship.

The most obvious deviation can be seen in the points (1) corresponding to deuteroxide ion catalysis. From the graph, it appears that the deuteroxide ion catalyzed reaction is slower than expected by a factor of 360 for the 4-methyl compound and by a factor of 1200 for the 4-isopropyl compound. This anomolous behavior, however, is not uncommon in a Brønsted relationship and although is not generally understood, it is discussed extensively in the literature.[18,19,20]

The deviation of the points for 4-amino-2,6-dimethylpyridine (4) and 2,6-dimethylpyridine (7) can be readily understood as examples of decreased reactivity due to steric hindrance of proton transfer by the ortho methyl groups of the buffer. Steric hindrance of this type has

been well documented for reactions involving rate-limiting proton abstraction from carbon.[16,21,22] In the base-catalyzed H-D exchange of isobutyraldehyde-2-d, 2,6-dimethylpyridine has been found to be less reactive than expected by a factor of almost 150[16] while for the base catalyzed deprotonation of 2-nitropropane, the observed rate is less than expected by a factor of only 5.[22] The steric effect of the ortho methyl groups retards the rate of H-D exchange in 1,4-dimethylpyridinium iodide by a factor of 5 and by a factor of 40 in the 4-isopropyl pyridinium iodide. The greater effect on the isopropyl compound than on the methyl compound is quite consistent with the idea of steric hindrance.

The slight deviation from the Brønsted line observed for the imidazole catalyzed exchange of the 4-methyl compound, while not appearing too significant, is not unprecedented. In the base-catalyzed H-D exchange of isobutyraldehyde-2-d, N-methylimidazole is three times less reactive than expected from a consideration of the reactivity of unhindered pyridines.[16] This decrease in the effectiveness of N-methylimidazole as a catalyst is attributed to the changes in internal geometry of the imidazole ring resulting from protonation of the molecule.

In the general base-catalyzed dehydrochlorination of 9-fluorenylmethyl chloride to give dibenzofulvene, both imidazole and N-methylimidazole are off the Brønsted line established by tertiary amines by an amount equivalent

to a fifty-fold reduction in catalytic effectiveness,[23] a result which would seem to support the idea that imidazoles do not correlate well with other bases. However, in a paper dealing with the amine catalyzed elimination from a β-acetoxy ketone, both imidazole and N-methylimidazole correlate quite well with the Brønsted line determined for tertiary amines.[24]

In light of the fact that no plausible argument has been put forth to explain the apparant inconsistency in behavior of imidazole and its N-methyl analog, it cannot be determined whether or not the small deviation observed for the imidazole point obtained in this study is in any way meaningful.

Transition State Structure

The striking feature of the exchange results listed in Table 8 and illustrated in Figure 5 is that although the reactivity order is the expected one on the basis of the electron-releasing character of a methyl group, the reactivity difference between the 4-methyl and 4-isopropyl compounds is quite small. The largest effect the substitution of two α-methyl groups for two protons has on the rate of exchange is observed in the case of deuteroxide ion catalysis. The reactivity ratio for the methyl compound relative to the isopropyl compound is 6.7. For the other bases, the ratio ranges from 2.7 to 1.2. Although the ratio decreases as the catalyst

becomes more weakly basic, changes are small and the ratio for imidazole (1.2) appears to be unusually small.

This rate-retarding effect of methyl groups ranks among the smallest known. The small size, however, provides considerable information about the structures of the transition states of the deprotonation reactions. Information from the literature on the magnitude of rate-retarding effects of methyl groups on other reactions involving deprotonation of carbon acids makesit clear that the effect of the methyl groups in the case of the pyridinium ion carbon acids is among the smallest on record.

The examples now considered include arenes, sulfides, sulfones, various carbonyl compounds and nitroalkanes. Where necessary, the reactive center is underlined.

The rates of base catalyzed hydrogen isotope exchange at the α-position of alkyl benzenes has been examined utilizing different base and solvent systems. These include potassium amide/ammonia, potassium cyclohexylamide/ cyclohexylamine, and potassium tert-butoxide/dimethyl-sulfoxide-t. The reactivity of the methyl group of toluene is greater than that of the isopropyl group of isopropylbenzene by factors ranging from 35 to 125. Table 10 records the results.

The very large effect of the methyl groups on the acidity of some thioalkylbenzenes in ammonia causes rates

Table 10. Relative Rates of Hydrogen Isotope Exchange of Alkylbenzenes at the α-Position.

Compound	NH_2K/NH_3 at 10°[a,b]	$c\text{-}C_6H_{11}NHK/c\text{-}C_6H_{11}NH_2$ at 50°[c,b]	$t\text{-}BuOK/CH_2TSOCH_3$ at 30°[d]
$C_6H_5CH_3$	34.5	125	43.5
$C_6H_5CH_2CH_3$	5	14.5	10
$C_6H_5CH(CH_3)_2$	1	1	1

[a] Reference 3.

[b] Deuterated substrate.

[c] Reference 25.

[d] Reference 26.

of amide ion catalyzed dedeuteration to vary over four powers of ten.[27]

$$C_6H_5SCD_3 \;/\; C_6H_5SCD_2CH_3 \;/\; C_6H_5SCD(CH_3)_2$$

$$10^4 \quad / \quad 10^2 \quad / \quad 1$$

The rates of deuteroxide catalyzed H-D exchange in D_2O-dioxane at the non-benzylic α-position of a series of alkylbenzylsulfones also are highly influenced by the presence of methyl groups.[28] Relative rates are indicated. It is suggested that this relative reactivity

$$C_6H_5CH_2SO_2\underline{CH}_3 \;/\; C_6H_5CH_2SO_2\underline{CH}_2CH_3 \;/\; C_6H_5CH_2SO_2\underline{CH}(CH_3)_2$$

$$10^4 \quad / \quad 10^2 \quad / \quad 1$$

may be inflated by as much as two powers of ten due to the presence of internal return. But that still leaves a relative reactivity of at least $10^2 / 10 / 1$.

The rates of methoxide catalyzed H-D exchange in methanol-O-<u>d</u> of a series of α-substituted methyl acetates were determined. Again, a reactivity difference of two powers of ten between an unsubstituted and dimethyl substituted carbon acid was observed.[29,30]

$$\underline{CH}_3CO_2CH_3 \;/\; CH_3\underline{CH}_2CO_2CH_3 \;/\; (CH_3)_2\underline{CH}CO_2CH_3$$

$$127 \quad / \quad 16.5 \quad / \quad 1$$

Similar results were obtained for deprotonation in a series of alkyl ketones in aqueous hydroxide.[31,32]

$(\underline{CH}_3)_2CO$ / $(CH_3\underline{CH}_2)_2CO$ / $(CH_3)_2\underline{CH})_2CO$

119 / 18 / 1

Rates of proton abstraction in methoxide/methanol of another pair of ketones show that a single methyl group retards the rate by a factor of 35.[33]

$C_6H_5CHClCO\underline{CH}_2CH_3$ / $C_6H_5CHClCO\underline{CH}(CH_3)_2$

35 / 1

Similar results are indicated for deprotonation reactions of 1,3-dicarbonyl compounds in aqueous hydroxide. The rate-retarding effect of a single methyl group varies from a factor of 68 to 136.[34]

$(CH_3CO)_2\underline{CH}_2$ / $(CH_3CO)_2\underline{CH}CH_3$

136 / 1

$CH_3CO\underline{CH}_2CO_2C_2H_5$ / $CH_3CO\underline{CH}(CH_3)CO_2C_2H_5$

102 / 1

$\underline{CH}_2(CO_2CH_3)_2$ / $CH_3\underline{CH}(CO_2CH_3)_2$

68 / 1

Finally, nitroalkanes have been studied in some detail. Two methyl groups retard the rate of deprotonation by deuteroxide ion by a factor of 87.[5]

$\underline{CH_3}NO_2$ / $CH_3\underline{CH_2}NO_2$ / $(CH_3)_2\underline{CH}NO_2$

87 / 16 / 1

However, when the base is acetate ion or water, two methyl groups have essentially no rate-retarding effect. That is, the unsubstituted and the dimethyl substituted nitromethanes react with these two bases at essentially the same rate.[5,6] This methyl group effect clearly ranks among the smallest for carbon acid deprotonation.

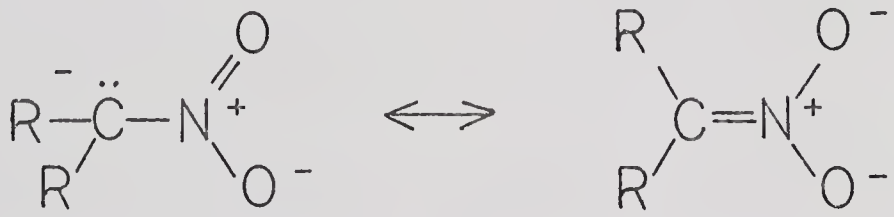
The rate retarding-effect of a methyl group on deprotonation at carbon has been rationalized in terms of the electron-releasing effect of the group. Negative charge builds up on a carbon as the transition state for deprotonation is approached; a methyl group by its inductive effect destabilizes the developing negative charge and thereby retards the rate of the reaction.

In order to understand the variation in the magnitude of the effect of the methyl groups with changes in the basicity of the catalyzing base, it is necessary to consider the effect of methyl groups on the equilibrium acidity of nitroalkanes. Methyl groups increase the

acidity of nitroalkanes, as the following pKa values indicate.[35,36]

	CH_3NO_2	$CH_3CH_2NO_2$	$(CH_3)_2CHNO_2$
pKa	10.2	8.5	7.7

The principal factor governing the pKa changes in the nitroalkanes is the resonance stabilization of the carbanions. Two important resonance structures can be drawn for a nitronate ion.



Because the negative charge can be contained on the electronegative oxygen atoms, the structure with a CN double bond is a more important contributor to the resonance hybrid than that with a single bond. The stabilizing effect of the methyl group on a double bond becomes more important than the inductive effect of the methyl group and so stabilization results.

The interesting variation in the methyl group effect found for nitroalkanes reacting with a series of bases is said to reflect changes in the extent of CH bond cleavage in the transition state.[5] In the presence of a strong base like hydroxide ion, the structure of the transition state for deprotonation is

more reactant-like and therefore the reactivity is determined by the inductive effect. With a weaker base, the structure of the transition state is closer to that of the product, the anion. As a result, the stabilizing effect of the methyl groups (as seen in the pKa values) becomes increasingly important.

This traditional interpretation has been challenged as a consequence of new results dealing with the kinetic and equilibrium acidities of arylnitroalkanes.[37,38] No evidence was found to support the idea of variable transition state geometries with variable base strength when the rates of deprotonation of arylnitroalkanes by a variety of bases were determined. Relative rates of deprotonation varied only by a small amount, regardless of whether a strong or weak base was employed as a catalyst.

It is not clear, however, whether the older interpretation for nitroalkanes really is invalidated by the new results. It is not clear if, in fact, a more product-like transition state requires more negative charge to reside on carbon. It is possible that in the arylnitroalkanes, a larger fraction of the negative charge may be borne by the nitro group leaving the amount of charge on carbon about the same regardless of variation in the structure of the transition state.[39]

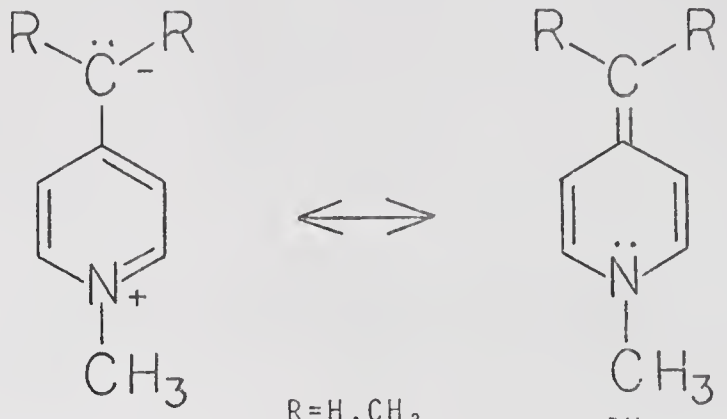
With this background it now is possible to interpret the kinetic results for the pyridinium ions. The key observation is that the rate-retarding inductive effect

of the two methyl groups is unusually small, regardless of the identity of the catalyzing base. This requires that the amount of charge on the carbon being deprotonated be small. Two interpretations are possible.

According to the first, the kinetic effect is small because the extent of CH bond cleavage in the transition state is small and the transition state structure closely resembles that of the reactants. This interpretation can be rejected because (a) it is not consistent with the large Brønsted β value of 0.75 which implies significant proton transfer, (b) the deprotonation reactions are expected to be endothermic and therefore the transition state should not resemble reactants in structure, and (c) the enormous activating effect of the heteroatom is not consistent with this view. The substrates "aza-p-xylene" and "aza-p-cymene" are isoelectronic with p-xylene and p-cymene, yet they are enormously more reactive than their hydrocarbon counterparts. This large difference in reactivity is strongly contradictory to a small amount of CH bond cleavage.

The second interpretation, more consistent with the small kinetic effect of the two methyl groups, is that in the transition state, there is substantial cleavage of the CH bond and a substantial fraction of the negative charge is delocalized into the heterocyclic ring. Charge neutralization involving the positively and negatively charged centers of the conjugate base is expected to

play a very important role in stabilizing both the transition state and the conjugate base as illustrated by the resonance structures for the conjugate base. It should



IV

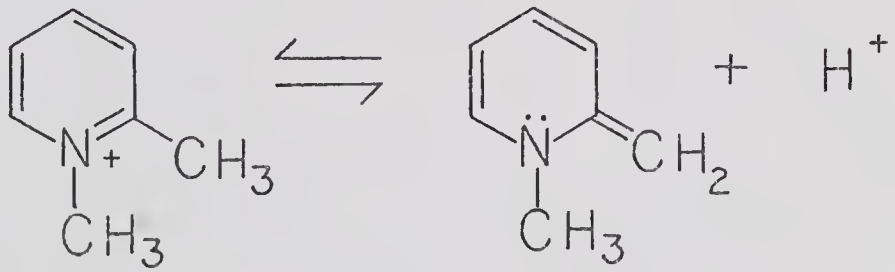
be noted that the uncharged structure IV is a kind of enamine with an olefinic carbon atom as part of the side-chain.

The small methyl group effect admirably supports this proposed transition state. Largely off-setting the inductive deactivating effect of methyl groups, which serves to make the isopropyl substrate less reactive than the methyl compound when the side-chain carbon bears a negative charge, is the well-known stabilizing effect of methyl groups bonded to an olefinic center. Because of the olefinic character of the reactive center in the transition state, the destabilizing effect of the methyl groups is substantially attenuated. Perhaps the carbon atom at the reactive center has the geometry of a flattened pyramid, i.e., the ligands bonded to the

carbon atom are approaching a state in which they lie in a plane defined by the heterocyclic ring.

It does not necessarily follow from the above description of the transition state that the equilibrium acidity of the isopropyl acid will be greater than that of the methyl acid. Methyl groups need not increase equilibrium acidities as in the case of the nitroalkanes. In fact, methyl groups usually decrease both kinetic and equilibrium acidities of carbon acids. Carbon acids containing cyano[40] and sulfonyl groups[41] show behavior of this type. Whether or not the isopropyl acid is more acidic than the methyl acid depends on how much negative charge resides on the side chain. The more the conjugate base resembles an olefin, the more likely it will be that the isopropylpyridinium ion will be the stronger acid.

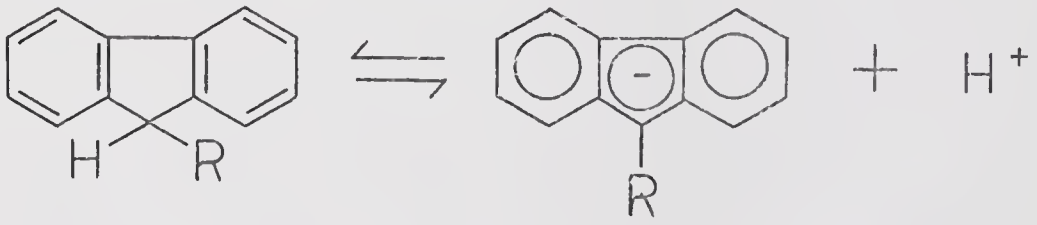
Although the equilibrium acidities of the two pyridinium ion carbon acids were not determined, a pKa value has been obtained for the 1,2-dimethylpyridinium ion



using an acidity function determined by a DMSO-water solution containing tetramethylammonium hydroxide. This

value is reported to be 20.0.[42] It seems reasonable to assume that the pKa for the 1,4-dimethylpyridinium ion is greater than 20 from the following two considerations. First, the kinetic acidity of 1,2-dimethylpyridinium iodide has been examined and was found to be greater than that for the 1,4-dimethyl compound.[43] It is unlikely that the equilibrium acidity order would be inverted. Second, when deprotonation takes place on a side-chain bonded to the heterocyclic ring, the equilibrium acidity of a 2-substituted pyridinium ion has been found to be greater than that for a 4-substituted one as long as no complicating steric factors exist.[44] For methyl substitution, the steric effect should not be significant.

In as much as the acid-strengthening (equilibrium) effect of methyl groups is uncommon, it is well to review another example, 9-alkylfluorenes. A number of molecular



explanations have been advanced; they will be reviewed.

The equilibrium acidities of a series of 9-substituted fluorenes in dimethylsulfoxide-water were determined.[45] It was found that contrary to the expectation that alkyl groups are electron releasing and destabilize carbanions in solution, 9-methylfluorene is more acidic than fluorene. Also noting that the acidity of the 9-alkylfluorenes

followed the order of $CH_3 > C_2H_5 > CH(CH_3)_2$, it was concluded that the acidity order could best be explained on the basis of an anionic hyperconjugation.

In a study by other workers,[46] it was suggested that alkyl group stabilization of carbanions occurs by dispersion interactions, a sort of internal van der Waals or London electronic correlation effect. Still others[47] attempted to explain the acidity order by suggesting a methyl group somehow increases charge delocalization.

In the latest study of the acidities of 9-alkylfluorenes[48] in cyclohexylamide/cyclohexylamine, results have been obtained consistent with other workers. The explanation proposed, however, is far more convincing.

It is suggested that the increased acidity of 9-methylfluorene is due to a stabilization by the methyl group resulting from a sigma bond strength change. In the fluorenyl anions, the negative charge is extensively delocalized and the deprotonated carbon is sp^2 hybridized. In 9-methylfluorene, this would mean a change from Csp^3-Csp^3 in the hydrocarbon to Csp^3-Csp^2 in the carbanion. In fluorene itself, the comparable bond change is Csp^3-H to Csp^2-H. There are abundant analogies to show that putting more s character into a carbon-carbon bond provides greater stabilization. This sigma bond stabilization effect is large enough to override the counteracting methyl inductive effect.

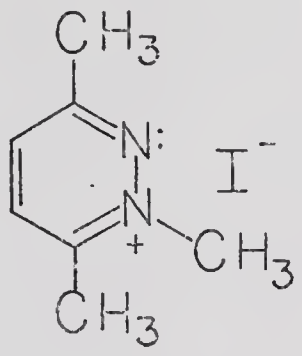
This argument was generalized in some later work[49] in a form quite applicable to the results of this present study. It was stated that in conjugated carbanions where only a partial negative charge is associated with the substituted carbon, the stabilizing effect of methyl substituents on trigonal carbanions dominates and alkyl substituents enhance acidity. In proton transfer transition states the central carbon is still pyramidal and hybridization stabilization is reduced. Similarly, less charge is delocalized than in the product carbanion. The more charge is concentrated at the central carbon, the more the inductive effect of alkyl substituents can dominate.

In summary, the kinetic acidities of 1,4-dimethylpyridinium iodide and 4-isopropyl-1-methylpyridinium iodide were determined and it was found that the effect of methyl substituents on the acidity was quite small. This small effect was explained on the basis of the olefin-like structure of the transition state for the proton transfer reaction and the stabilizing effects of the methyl groups on a double bond in contrast with the destabilizing inductive effect of the methyl groups on a negative charge. It would be of interest to have the equilibrium acidities of these two molecules measured so as to conclusively establish the role played by the methyl groups in determining the stability and structure of the conjugate bases of these two molecules.

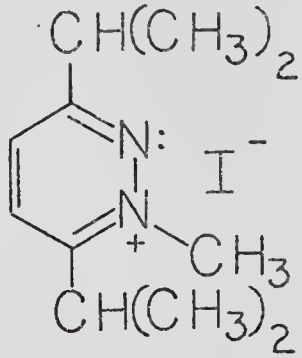
CHAPTER 3

ALKYL GROUP HYDROGEN-DEUTERIUM EXCHANGE IN 1,3,6-TRIMETHYL- AND 3,6-DIISOPROPYL-1-METHYL-PYRIDAZINIUM IODIDES

The kinetics of H-D exchange in the 6-alkyl group of 1,3,6-trimethylpyridazinium iodide (V) and 3,6-diisopropyl-1-methylpyridazinium iodide (VI) in buffered D_2O solutions of 1.0 M ionic strength were compared at 75.0 ± 0.1°. The exchange reactions were followed by measuring the change in the integrated areas of the appropriate nmr signals.



V



VI

In order to approximate their reactivity difference, the two compounds were dissolved in bicarbonate-carbonate buffer solutions and compared by nmr. In a solution of 0.42 M in bicarbonate ion and 0.20 M in carbonate ion, the acidity of the 6-methyl group of V was sufficient to cause immediate and complete exchange simply on mixing. No signal for the 6-methyl group could be observed in the

nmr. The acidity of the 6-isopropyl group of VI was much less and the exchange reaction in a 0.10 M bicarbonate - 0.15 M carbonate buffer solution, pD = 10.75, had a half-life of approximately 200 minutes.

The two compounds were next compared in a 0.075 M $D_2PO_4^-$ - 0.15 M $DPO_4^=$ buffer solution, pD = 7.34. In this buffer solution, the 6-methyl group of V was less reactive but not dramatically so. Exchange could be observed taking place in the nmr probe at 35° during the course of recording the spectrum. The 6-isopropyl group reactivity of VI had decreased to the point where the exchange reaction at 75.0° would no longer take place at a convenient rate.

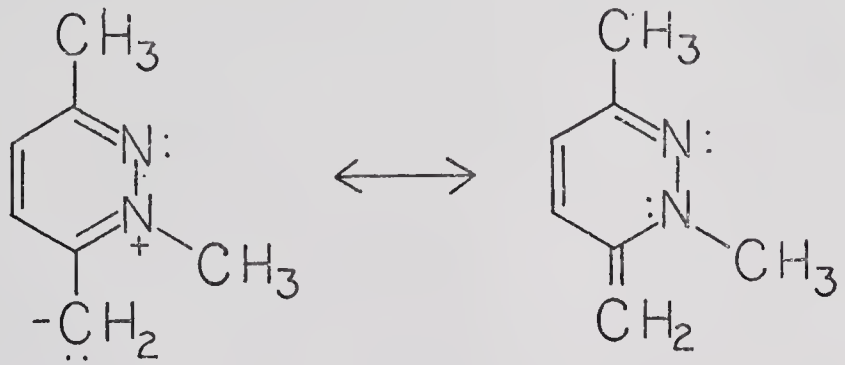
In an effort to approximate the 6-methyl group reactivity, compound V was next studied in a 0.25 M formic acid - 0.25 M formate ion buffer, pD = 4.15. In this buffer at 75.0°, the exchange reaction proceeded with a half-life of approximately 300 minutes.

Assuming the exchange reaction to proceed by specific base catalysis, the reactivity ratio of the two compounds can be calculated from the buffer pD's and reaction half-lives. Treating the kinetic data in this fashion, it is found that the 6-methyl group of 1,3,6-trimethylpyridazinium iodide is more acidic than the 6-isopropyl group of 3,6-diisopropyl-1-methylpyridazinium iodide by a factor of 3×10^6.

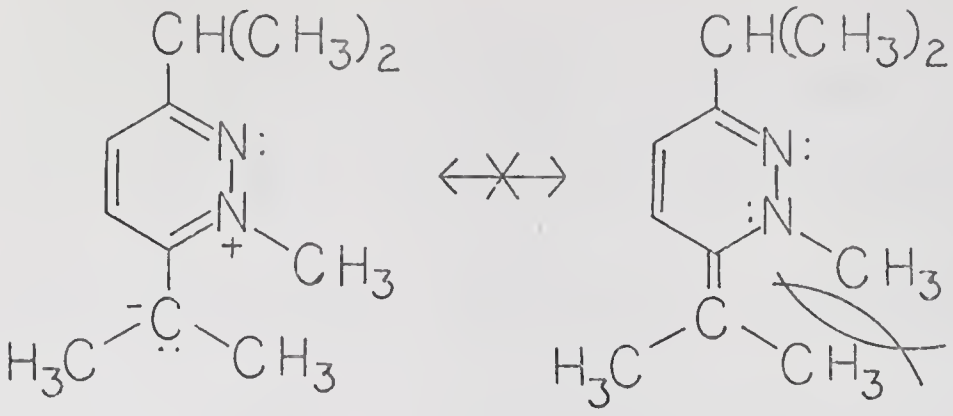
Obviously, if the reaction is general base catalyzed and catalysis by the buffer base makes a substantial

contribution to the exchange rate of the methyl compound, the above acidity ratio would be decreased. It seems reasonable to assume, however, that this ratio would not be reduced to a point of decreased significance.

Although a thorough investigation has not been conducted, it would appear the primary reason for this large difference is steric inhibition of resonance.[50] The negative charge on carbon in the transition state for deprotonation can be delocalized in the case of the methyl compound by donation to the ring and the positively charged nitrogen. Such resonance stabilization is shown for the intermediate resulting from deprotonation.



In the isopropyl compound, the steric interaction of the ortho methyl and isopropyl groups prevents the isopropyl group from achieving the geometry necessary for maximum orbital overlap and charge delocalization. Again the intermediate is shown.


CH(CH3)2
N:
N
+
CH3
C
H3C
CH3
CH(CH3)2
N:
N
CH3
C
H3C
CH3

CHAPTER 4

EXPERIMENTAL

Instrumentation

Nuclear magnetic resonance spectra were recorded on a Varian Associates Model A-60A instrument. Melting points were obtained with a Thomas-Hoover Unimelt melting point apparatus. Measurements of pD were determined on a Beckman Model 1019 Research pH meter equipped with a Corning (476050) semi-micro combination electrode. Both measurements of pD and kinetic runs were carried out in a Lauda/Brinkmann Model K-2/R constant temperature circulator.

Chemicals

All common laboratory chemicals, unless specified to the contrary, were reagent grade and from various suppliers. Deuterium oxide (99.8 percent) was obtained from Columbia Organic Chemicals.

Stock Solutions

Stock solutions of dilute DCl were prepared by diluting concentrated HCl with D_2O and standardized by potentiometric titration using standardized NaOH.

Stock solutions of dilute potassium deuteroxide were prepared by dissolving weighed quantities of reagent grade

KOH in D_2O. The solutions were standardized by potentiometric titration using primary standard grade potassium hydrogen phthalate.

Nucleophiles

Aldrich Chemical Company gold label grade 2,2,2-trifluoroethanol and Mallinckrodt reagent grade sodium acetate were used directly. Pyridine obtained from Mallinckrodt Chemical Works, was dried over sodium and distilled from zinc powder (bp 114-116°; lit[51] 115.5°). Eastman Organic Chemicals 2,6-dimethylpyridine was likewise dried over sodium and distilled from zinc powder (bp 142-143°; lit[51] 143°). Imidazole, purchased from Matheson Coleman and Bell, was recrystallized from hexane (mp 89-91°; lit[51] 90°). Reilly Tar and Chemical Corp. 4-aminopyridine was purified by vacuum sublimation and recrystallized from benzene (mp 157-160°; lit[51] 158°). The method of Evans and Brown[52] was used to prepare 4-amino-2,6-dimethylpyridine which was purified by successive vacuum sublimations (mp 190-191°; lit[52] 191-192°). The purification of phenol was accomplished by adding benzene to phenol, liquified reagent, obtained from Matheson Coleman and Bell, and distilling first a benzene-water azeotrope, then excess benzene and finally the phenol at reduced pressure and under nitrogen (bp 90°/25 torr; lit[53] 90°/25 torr). Calcium hydroxide was prepared according to the procedure of Bates, Bower, and Smith[7] by heating

well-washed calcium carbonate in a platinum crucible at approximately 1000° C with a Meeker burner for one-hour intervals until a constant weight is obtained. The freshly prepared oxide was then slowly added to water, the solution heated to boiling, cooled and filtered. The solid was then oven dried and crushed to a finely granular state for use. Calcium deuteroxide was prepared by dissolving calcium hydroxide in D_2O.

Substrates

Pyridinium iodides

1,4-Dimethylpyridinium iodide.--4-Picoline, obtained from Matheson Coleman and Bell, was distilled from zinc powder and dissolved in methanol. Methyl iodide was slowly added. The mixture was then refluxed for one hour, evaporated on a rotovap and the resultant solid recrystallized from absolute ethanol (mp 153-154°; lit[54] 153-153.8°). The compound was stored under vacuum.

4-Ethyl-1-methylpyridinium iodide.--The compound was prepared by dissolving freshly distilled 4-ethylpyridine, obtained from Aldrich Chemical Company, in ethanol, adding methyl iodide and refluxing one hour. The resulting salt was recrystallized from an ethanol-ethyl acetate mixture (mp 109°; lit[54] 109-110°). The compound was stored under vacuum.

4-Isopropyl-1-methylpyridinium iodide.--The liquid 4-isopropylpyridine, purchased from K and K Laboratories,

Inc., was first fractionally distilled, the portion distilling at 181-182° collected. The distillate was then dissolved in methanol and treated as above with methyl iodide. After reflux the solution was cooled and the excess methyl iodide and methanol were evaporated with as little heating as possible to facilitate the evaporation. The crude salt was then recrystallized by dissolving in excess ethanol at room temperature and then inducing crystallization by slowly adding small portions of ethyl ether (mp 125.5-128.5°; lit[54] 117-120° dec). The compound was stored under vacuum. Analysis: Calcd. for $C_9H_{14}NI$: C, 41.08; H, 5.36; N, 5.32; I, 48.23. Found: C, 41.09; H, 5.38; N, 5.28; I, 48.24.

Pyridazinium iodides

1,3,6-Trimethylpyridazinium iodide.--The procedure of Overberger, Byrd, and Mesrobian[55] was followed for the synthesis of 3,6-dimethylpyridazine. The pyridazine and methyl iodide were added together neat and the resulting solid recrystallized from acetone (mp 119.5-120.5°; lit[56] 118.5-119.5°).

3,6-Diisopropyl-1-methylpyridazinium iodide.--The compound 3,6-diisopropylpyridazine (mp 75-76.5°) was obtained from White.[57] The pyridazine was dissolved in methyl iodide and gently refluxed for two hours. The resultant salt was recrystallized from acetone/ether (mp 156-158°).

Preparation of Solutions

Either three or ten milliliters of solution were prepared for each run in an appropriate sized volumetric flask.

Substrate was weighed on an analytical balance along with a corresponding molar amount of internal standard and transferred to the volumetric flask.

Accurate volumes of stock acid or base were delivered by means of Hamilton Microliter syringes.

Depending on the intended concentration, solubility, or physical characteristics, the appropriate nucleophile was either accurately weighed on an analytical balance and transferred directly to the flask or first dissolved in D_2O to make a stock solution from which the proper volume was then withdrawn and transferred by syringe. For the 4-amino-2,6-dimethylpyridine runs, not only was it necessary to make a D_2O solution first, but it was also necessary to add an equivalent of DCl to get the solid to dissolve easily. The DCl was then later neutralized with KOD solution.

Weighed amounts of potassium chloride were added to each flask to obtain an ionic strength of 1.00 M and the solutions were finally diluted to mark with D_2O.

Kinetic Procedure for H-D Exchange

Kinetics were obtained by two methods. The first method, by which a majority of the work was done, involved

the use of three milliliters of solution. Upon completion of the solution preparation, approximately one milliliter was withdrawn and transferred to an nmr tube which was then flushed with nitrogen and sealed. The remainder of the solution was stored in the flask, under nitrogen, for later comparison and pD measurements.

A proton nmr spectrum of the solution in the sealed tube was recorded. The nmr tube was then immersed in a constant-temperature circulating bath which had been previously set at the desired temperature using a National Bureau of Standards Certified thermometer. Periodically, the nmr tube was removed from the bath, immediately quenched by immersion in ice water, and the proton nmr spectrum of the solution was recorded.

In mixtures with a high deuteroxide concentration, it was apparent that the temperature of the nmr probe was sufficient to maintain the exchange reaction. For these cases, a second method was employed. From ten milliliters of stock solution, two milliliters were withdrawn by syringe and stored, under nitrogen, for pD measurements. The remaining solution was immersed in the constant-temperature bath in a 10 ml volumetric flask that was fitted with a rubber septum. Periodically, 0.9 ml of solution was withdrawn by syringe and injected into a test tube containing 0.1 ml of a 1.2 M DCl quench solution. This neutralized solution was then transferred to an nmr tube and its proton nmr spectrum recorded.

Reactions were followed a minimum of 1.5 half-lives by measuring the change in the integrated area of the nmr signal of the proton(s) of interest with respect to that of a non-exchanging proton in the reaction mixture. The integrals of proton signals were measured in a minimum of five successive sweeps and the average value was taken.

In practically all the runs, an internal standard external to the substrate was used. For runs involving the 1,4-dimethylpyridinium iodide, tetramethylammonium bromide was added as an internal standard. If 4-isopropyl-1-methylpyridinium iodide were present, it was necessary, due to peak overlap, to change to sodium acetate as an internal standard. Although acetate ion was not an ideal standard since it does promote exchange, it does so slowly and once a rate constant was obtained for this exchange, it could be easily calculated out of the particular reaction kinetics.

In the case of 2,6-dimethylpyridine, it was found necessary to use the ring protons of the substrate as an internal standard since catalysis by acetate ion was greater than by 2,6-dimethylpyridine. Substrate ring protons were also used as internal standards for all runs involving 3,6-dimethyl- and 3,6-diisopropyl-1-methyl-pyridazinium iodide.

For each kinetic run a plot was made of the quantity $[\log(A/A_{std})_t - \log(A/A_{std})_{t_0}]$ versus time where $(A/A_{std})_t$

is the ratio of the integrated area of the reacting proton(s) to the integrated area of the internal standard at a given time, t, and $(A/A_{std})_{t_0}$ is the ratio of the two areas at the start of the run, i.e., t_0. A pseudo-first-order rate constant was then calculated from each plot by visually fitting the best straight line through the points and applying equation 16.

$$k\psi = \frac{-2.3[\log(A/A_{std})_{t_1} - \log(A/A_{std})_{t_2}]}{t_1 - t_2} \qquad (16)$$

pD Measurements

Measurements of pD were performed on all solutions employed in the various kinetic runs. NBS standard buffers were prepared as described by Bates.[58]

For pD measurements at 75.0 ± 0.1°, the electrode was first allowed to equilibrate in 4 M KCl at 75.0 ± 0.1° for a minimum of 20 minutes. The meter was then standardized at pH 6.852 against the NBS phosphate buffer by adjusting the standardization control on the meter.[58] When the pD of an alkaline solution was being measured, the meter was linearized at pH 8.905 against an NBS borax buffer by adjusting the temperature control on the meter.[58] When the sample solution being measured was acidic, the meter was linearized at pH 4.145 against an NBS phthalate buffer.[58] Standardization and pD measurements were carried out without allowing the electrode to cool

by rinsing and storing of the electrode in distilled water at 75.0 ± 0.1° between actual measurements.

For pD measurements at 50.0 ± 0.1°, the procedure was exactly the same with the meter being standardized against an NBS phosphate buffer value of pH 6.833 and linearized against a borax buffer value of pH 9.011.[58] No acidic pD values were measured at this temperature.

At 25°, no temperature equilibration was necessary for the electrode. Once again phosphate (pH 6.865) and borax (pH 9.180) buffers were used for standardization and linearization, no acidic pD measurements being made.[58]

Since the pH meter was standardized and linearized against standard proteo buffers, it was necessary to add a correction to the meter readings obtained for the various samples to arrive at accurate pD values. For pD measurements at 25°, the pD value is reported by Bates to be obtained by adding 0.41 to the meter reading.[59] For pD measurements at 75°, this correction factor is reported to be 0.35.[60] For pD measurements at 50°, a value of 0.38 is obtained by simple interpolation for the above reported values.

The concentration of deuteroxide ion was calculated using the relationship $pOD = pKw^{D} - pD$. The values used for pKw^{D}, the dissociation constant for deuterium oxide, as well as the factors for converting pH meter readings to pD, may be found in Table 11.

Table 11. Dissociation Constants for D_2O and pH to pD Conversion Factors at Several Temperatures.

T, °C	pKw^D [a]	pH→pD
25	14.869[8]	0.41[59]
50	14.103[8]	0.38[b]
75	13.526[c]	0.35[60]

[a] These values are uncorrected for salt effects which are expected to be small.[61]

[b] From interpolation.

[c] Calculated from reported data.[8,9]

Values for the respective buffer pKa determinations were obtained from the pD measurements by the formula

$$pKa = pD + \log\frac{[BD^+]}{[B]}$$

Control Runs

Although the presence of an internal standard, agreement of pD measurements on original and recovered solutions, and the linearity of the pseudo-first-order kinetic plots indicated the absence of important complicating factors, control runs were carried out to determine the stability of both the 4-methyl- and 4-isopropylpyridinium iodides under various conditions.

The two pyridinium iodides were first dissolved in 0.10 M DCl solutions with an acetic acid internal standard and heated at 75° to determine their stability and, if possible, measure any exchange catalyzed by D_2O acting as the buffer base. No exchange, as evidenced by the broadening of the 4-methyl singlet or the emerging of a singlet between the 4-isopropyl gem.-dimethyl doublet, could be detected in the nmr. These nmr spectral changes are a more sensitive indication of initial deuterium substitution than change in the integral ratios.

The solutions were heated until the change in the integral ratios of substrate to internal standard reached 10 percent. In neither case were there observed the above-mentioned spectral changes indicative of exchange.

The appearance of a precipitate was also noted in both solutions. The change in the integral ratio was, therefore, attributed totally to degradation of substrate. For the 4-methyl compound, heating for a period of seven days produced the 10 percent degradation while for the 4-isopropyl compound, heating for a period of fourteen days was required to produce this same percent change.

Proteo control runs were then carried out in three different buffers to verify the stability of the two pyridinium iodides in basic solution. Previously used buffer solutions were duplicated using H_2O in place of D_2O and the mixtures were heated for the equivalent of ten half-lives. For each buffer, the most basic conditions previously employed were the conditions duplicated for the control runs. Although kinetic runs were never carried out with the 4-isopropyl compound in 4-amino-2,6-dimethylpyridine buffer, a control run using this buffer was carried out for comparison purposes. Details of these control runs, the solution compositions, heating times, and observed pH changes are contained in Table 12.

Degradation of substrate as measured by loss of the signal for the 4-alkyl group relative to the signal of acetate ion internal standard, was less than 10 percent in all cases. The pH changes were also small (.035 or less) for all but the 2,2,2-trifluoroethanol buffer. For this buffer, the pH change was substantially larger,

Table 12. Solution Composition Data and Results for Proteo Control Runs.

Buffer	pD[a]	[B],M	[BH^+],M	4-Methyl t,[b] min	4-Methyl ΔpH[c]	4-Isopropyl t,[b] min	4-Isopropyl ΔpH[c]
$Ca(OH)_2$	11.6	1.19×10^{-2}	---	20	.035	140	.022
4-Amino-2,6-dimethyl-pyridine	10.5	9.89×10^{-2}	9.98×10^{-3}	220	.015	2000[d]	.015
2,2,2-Trifluoroethanol	9.9	1.59×10^{-3}	1.71×10^{-2}	210	.196	1750	.728

[a] pD value for the same buffer in D_2O at 75°.

[b] Indicated heating time corresponds to 10 half-lives for H-D exchange.

[c] Measured at 25°; ΔpH = pH(initial) - pH(after heating).

[d] Buffer not employed in H-D exchange studies with this substrate.

being 0.196 for the 4-methyl compound, and 0.728 for the 4-isopropyl compound. In addition, the nmr spectra of these solutions, although indicating less than 10 percent change in the integral ratio values, also showed unidentified peaks similar to and emerging 10 to 20 Hertz downfield from the expected nmr signals. As a result, the values of the rate constants obtained using this buffer are uncertain.

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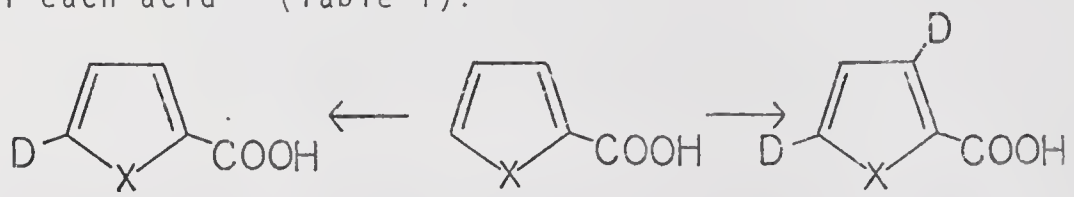
PREVIOUSLY PUBLISHED INVESTIGATIONS

The material contained in this section has been separated from the main text as it has already been published. It consists of two parts. The first, "Convenient Preparations of Mono- and Dideuterated 2-Furoic and 2-Thiophenecarboxylic Acids," has been published in the Journal of Heterocyclic Chemistry and is presented here exactly as it appears in the literature. The second part, "Nucleophilicities of Compounds with Interacting Electron Pairs. Diazine-Catalyzed Ester Hydrolysis," was published in Tetrahedron Letters. In as much as Tetrahedron Letters does not publish experimental sections, the original article will be presented along with experimental details.

Convenient Preparations of Mono- and Dideuterated 2-Furoic and 2-Thiophenecarboxylic Acids*

2-Furoic[1] 1a and 2-thiophenecarboxylic[2] 1b acids and their derivatives are useful starting materials for the preparation of furans and thiophenes containing various side-chains, including compounds of biological interest.

We wish to report convenient and very simple preparations of mono- and dideuterated forms of these two acids. Deuterium labeling was achieved by hydrogen exchange reactions either at position 5 (2) or at positions 3, 5 (3) of each acid (Table 1).



a, X=O
b, X=S

The following conditions were found to be optimum for monodeuteration (method A). The appropriate carboxylic acid was heated at 165° in a deuterium oxide-carbonate buffer (pD ~10). The monodeuterated product 2 was obtained on cooling and acidifying the reaction mixture.

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* Published in the Journal of Heterocyclic Chemistry, 8, 331 (1971).

Table 1. Deuterated 2-Furoic and 2-Thiophenecarboxylic Acids Prepared by Hydrogen-Deuterium Exchange[a]

Deuterated Acid	Method	T, °C	Time	%3-D	%5-D	% Yield Acid
2a	A	165	6 hr.	--	95	52
3a	B[b]	250	45 min.	19	28	26
2b	A	165	5 hr.	--	~100	63
3b	B[b]	250	2 hr.	32	32	63

[a] Nmr analyses of percent deuteration have about a 3% uncertainty, H-4 being used as an internal standard.

[b] >90%D in the COOD group initially.

Nmr analyses revealed that in each case the H-5 signal of the acid had almost completely disappeared (>95 percent D); the remainder of the spectrum was that of a simple AB system. Note that the chemical shift order (decreasing τ values) for 1a is H-4>H-3>H-5[3] but for 1b it is H-4>H-5>H-3.[2,4] Mass spectral analysis indicated the formation of less than 6 percent dideuterated acid. While it was not possible to determine clearly the position of the second deuterium atom, the results given below suggest that it is position 3.

Deuteration at the 3,5 positions was conveniently effected by heating the dry acid containing the COOD group at 250° (method B). Deuterium was introduced into the carboxyl group by recrystallizing 1 from deuterium oxide. The amount of deuterium in the carboxyl group was determined by nmr analysis of a methylene chloride solution. In the case of 3b the amount of deuterium introduced into the 3,5 positions was that expected for a statistical distribution of deuterium among these two positions and the carboxyl group. Deuteration was not statistical in the case of 3a, the 5-position underwent more exchange than the 3-position. Statistical distribution of deuterium was not observed since a shorter reaction period was necessary due to the extensive decarboxylation of 1a at the temperature employed.

Although higher degrees of deuteration could be achieved in method B, no attempt was made in this

direction. By relabeling the carboxyl material, additional hydrogen-deuterium exchange would result.

Experimental

Materials.--2-Furoic acid (1a), m.p. 133-134°, Matheson Coleman and Bell and thiophene-2-carboxylic acid (1b) m.p. 127-128° (Aldrich Chemical Co.) were used as received. Deuterium oxide (>99 percent) was supplied by Columbia Organic Chemicals Company. A Parr Instrument Company Monel Bomb was employed.

Hydrogen-Deuterium Exchange

Method A. Exchange at H-5.--Deuterium oxide (16 ml.) was added to an equimolar mixture of 0.008 M of 1a or 1b and sodium carbonate. The solution having pD~10 was heated in a bomb at 165°. After cooling, the reaction mixture was acidified with dilute hydrochloric acid and the precipitate was collected. Recrystallization from proteo water gave the corresponding carboxylic acid-5-d. Nmr analyses were obtained on methylene chloride solutions. Results are summarized in Table 1. Mass spectral analysis of 2a showed d_0=8.0 percent, d_1=86.2 percent, and d_2=5.8 percent; 2b showed d_0=3.6 percent, d_1=95.0 percent, and d_2=1.4 percent.

Method B. Exchange at H-3,5.--2-Furoic acid-O-d or 2-thiophenecarboxylic acid-O-d (2.0 g) was heated in a bomb at 250°. The product obtained from the cooled

bomb was dissolved in methylene chloride for nmr analysis. Prior to nmr analysis of 2a, the solid was gently warmed to remove furan formed by decarboxylation. Results are given in Table 1. The dideuterated products were recrystallized from proteo water before mass spectral analysis: 3a showed d_0=59.9 percent, d_1=34.6 percent, d_2=5.5 percent; 3b showed d_0=46.2 percent, d_1=43.6 percent, d_2=10.2 percent.

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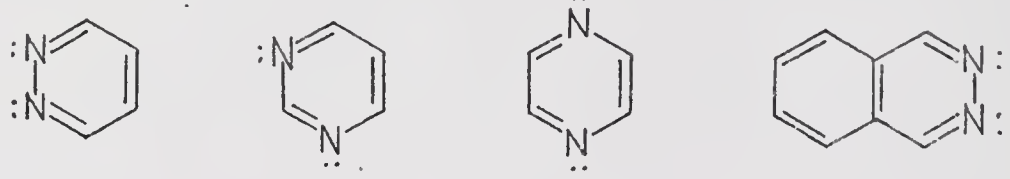
Nucleophilicities of Compounds with Interacting Electron Pairs. Diazine-Catalyzed Ester Hydrolysis*

Pair-pair electron repulsion has been suggested to be an important factor responsible for the abnormally high reactivity of nucleophiles such as $R\ddot{O}\ddot{O}^-$ toward some electrophiles.[1] Recently, it has been suggested that widely separated electron pairs may interact strongly. Thus, molecular orbital calculations[2] and photoelectron spectroscopy[3,4] indicate that the unshared electron pairs of the diazines pyridazine (I), pyrimidine (II) and pyrazine (III) interact strongly. Interactions are transmitted both through space and through bonds.



I II III IV

This recent evidence for electron pair repulsion prompted us to determine whether the diazines and a benzolog, phthalazine (IV), would show an enhanced reactivity toward 2,4-dinitrophenyl acetate (DNPA); these compounds are expected to act as nucleophilic catalysts for the hydrolysis of this ester.[5] A

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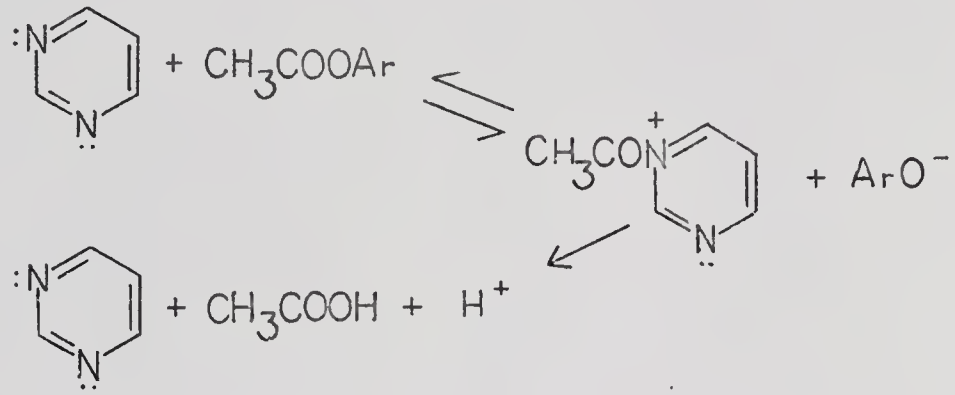
* Published in part in Tetrahedron Letters, 189 (1972).

representative hydrolysis pathway is shown in Scheme 1. This ester was selected for study because it was expected to react with the compounds of interest at convenient rates and because it is known to show large rate enhancements[5] in its reactions with nucleophiles such as $R\ddot{O}\ddot{O}^-$.

Scheme 1



The approach adopted is a standard one. The reactivities of I-IV were estimated from their pKa values using an established[5] Brønsted reactivity-basicity correlation. The estimated reactivities then were compared with experimental reactivities obtained under similar experimental conditions. Differences between observed and estimated nucleophilicities provide a measure of rate enhancements.

The reference Brønsted correlation was established using known rate constants for the reactions of DNPA with 4-methylpyridine (V), pyridine (VI) and nicotinamide (VII) in water at 25.0° and 1.0 M ionic strength.[5] (In order to check this method, the reactivity of nicotinamide

toward DNPA was determined. The second-order rate constant obtained is only 6 percent less than the reported value.)

The reactivities of I-IV toward DNPA at 25.0° were measured spectrophotometrically at 400 nm in 1:1 acetic acid-acetate ion buffers (3.2-20 x 10^{-3} M, total buffer) maintained at 1.0 M ionic strength with KCl. The concentration of DNPA was varied over the range 1-15 x 10^{-5} M. Pseudo-first-order rate plots were linear over at least 4 half-lives and second-order rate constants, k_2, were not dependent on the initial concentration of DNPA, showing that the reverse of the first step in Scheme 1 is kinetically unimportant. Rate constants were calculated according to equation 1.

$$k\psi = k_2[B]_t \cdot \frac{Ka}{[H] + Ka} + 3.4 \times 10^{-2}[CH_3CO_2^-] + 1.2 \times 10^{-5}[H_2O] \qquad (1)$$

Corrections for acetate ion and water catalyzed ester hydrolyses were made using known rate constants;[5] they were $\leq$ 13 percent of $k\psi$. The concentration of nucleophile in the free base form was calculated from a knowledge of the total concentration of nucleophile, $[B]_t$, its Ka and a measured pH. Titrations were used to obtain pKa values for I and IV at 25.0° and 1.0 M ionic strength; values for II and III are taken from the literature.[6] Results are summarized in Table 1.

Table 1. Conditions and Results of the Hydrolysis of DNPA at 25.0°.

Compound	pKa	No. of Runs	Free Nucleophile Concn. Range, M	k_2, M^{-1} min^{-1}
I	2.44	6	0.00493 - 0.0257	4.35 ± 0.26
II	1.23	4	0.216 - 0.648	$2.84 \pm 0.30 \times 10^{-2}$
III	0.65	3	0.260 - 0.520	$1.68 \pm 0.08 \times 10^{-2}$
IV	3.54	6	0.000470 - 0.00182	$5.06 \pm 0.34 \times 10^{1}$

Figure 1 shows the Brønsted plot of nucleophilic reactivity versus pKa established by pyridine nucleophiles. The results for diazines II and III lie on this line and do not show an enhanced reactivity toward DNPA. But diazines I and IV show rate enhancements by a factor of 12. (Rate and equilibrium constants for the diazines are statistically corrected to reflect reaction at two equivalent nitrogen atoms, i.e., $k_2/2$ and 2Ka are used in Figure 1.)

It is clear from our results that I and IV can show reactivities which exceed those predicted by their basicities but it is curious that no special nucleophilicities are found for II and III. It will be of interest to determine whether rate enhancements can be demonstrated for II and III toward other electrophiles.

Experimental

Instrumentation. Ultra-violet absorption spectra were obtained on a Zeiss Model PMQ II spectrophotometer. Constant temperature in the cell holder was maintained by connection to a Lauda/Brinkman Model K-2/R constant temperature circulator. Temperature in the cuvettes was checked by an NBS certified thermometer and found to be ± 0.5°. Measurements of pH were determined on a Beckman Model 1019 Research pH meter equipped with a Corning (476050) semi-micro combination electrode. Melting points

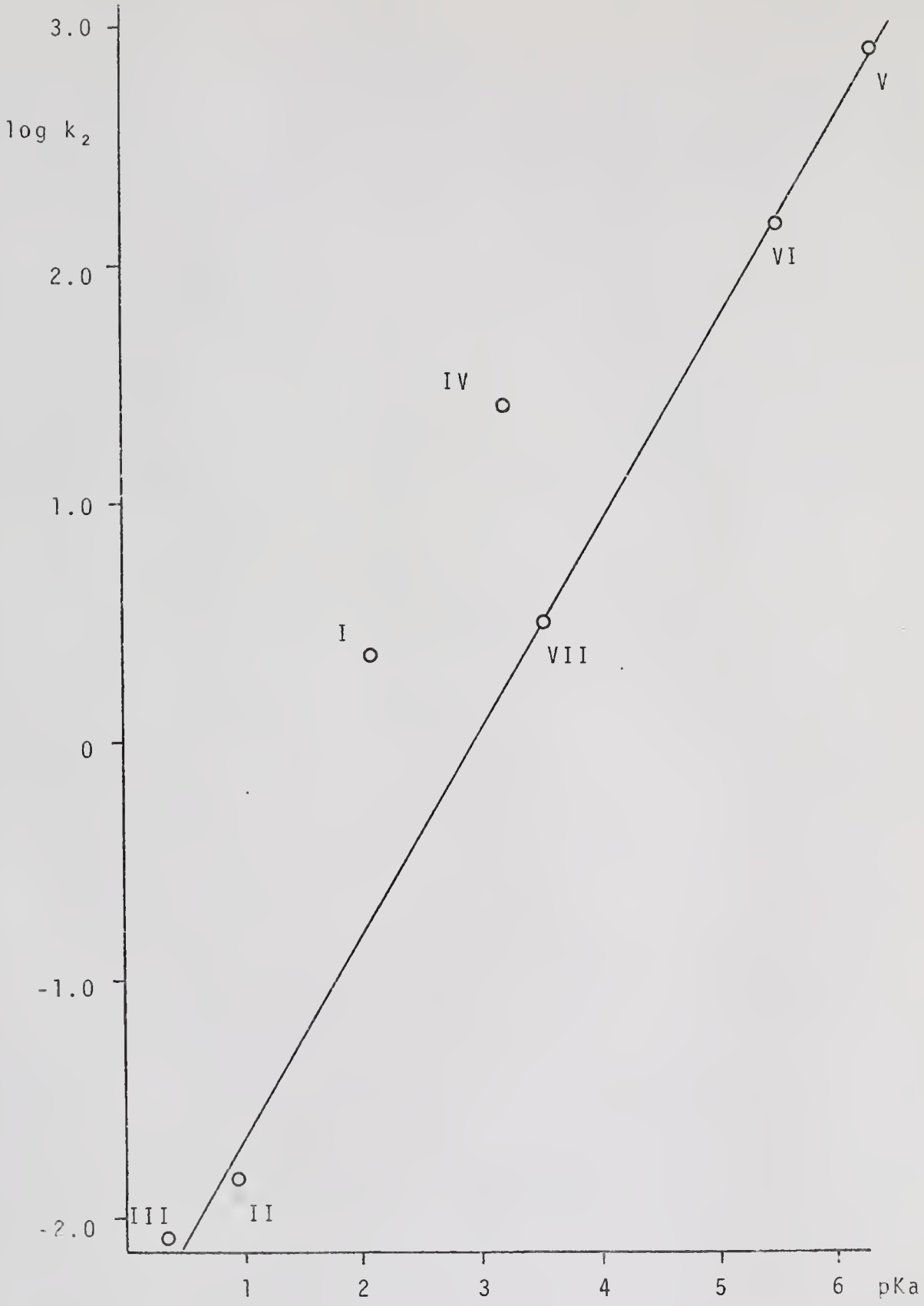


Figure 1. Brønsted plot of pKa versus log k_2 for diazines I-IV and pyridines V-VII reacting with DNPA.

were obtained with a Thomas-Hoover Unimelt melting point apparatus and are uncorrected.

Chemicals. All heterocycles used as nucleophiles were commercially available from various suppliers and were used as received with the exception of phthalazine which was first recrystallized from ether mp 90° (lit[7] mp 90-91°). The procedure of Bender and Nakamura[8] was used for the synthesis of 2,4-dinitrophenyl acetate. The ester was recrystallized from ethyl acetate/petroleum ether, mp 70.5-71.5 (lit[7] mp 72°). All common laboratory chemicals were reagent grade and were obtained from various suppliers.

Kinetics of Acetylation of 2,4-Dinitrophenyl Acetate. Pseudo-first-order rate constants, $k\psi$, for reactions between nitrogen heterocycles and 2,4-dinitrophenyl acetate in aqueous solution at 25.0° and 1.0 M ionic strength were obtained by monitoring the formation of 2,4-dinitrophenol at 400 nm in the ultra-violet spectrum.

Buffer solutions were of two types. One type, used for phthalazine and pyridazine, consisted of a 2:1 molar mixture of heterocycle and HCl in a solution made 1.0 M in ionic strength by the addition of KCl. For the weaker bases pyrimidine and pyrazine, and in some instances phthalazine and pyridazine, solutions consisted of heterocycle in a 1:1 acetic acid-acetate ion buffer solution that was also made 1.0 M in ionic strength by

the addition of KCl. The KCl solutions, with and without acetate buffer, were also employed as optical blanks.

Reactions were initiated by syringing a measured amount of the ester, in a water-acetonitrile mixture (4:1 by volume), into a cuvette thermostated inside the spectrophotometer.

The observed rate constant, $k\psi$, was experimentally determined by applying the equation

$$k\psi t = 2.303 \log \frac{[A_\infty - A_o]}{[A_\infty - A_t]}$$

or

$$-\log [A_\infty - A_t] = \frac{k\psi}{2.303} t - \log [A_\infty - A_o]$$

where A_∞ is the absorbance at infinite time, A_t is the absorbance at any time, t, and A_o is the absorbance at time zero. The observed rate constant, $k\psi$, is obtained merely by plotting $-\log[A_\infty - A_t]$ versus t, the slope of the line being $k\psi/2.303$.

The observed rate constant was corrected to eliminate reaction by water and acetate ion by multiplying the known second-order rate constants for both water and acetate ion[5] by their respective concentrations and subtracting from the experimentally determined rate constant.

Measurements of pH were made on all solutions and the concentration of unprotonated heterocycle was

calculated by multiplying the total concentration of heterocycle in solution by the fraction Ka/([H]+Ka).

Second-order rate constants were then obtained by dividing the corrected $k\psi$ by the concentration of unprotonated heterocycle. (See equation 1.)

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BIOGRAPHICAL SKETCH

Harvey Lewis Jacobson was born on February 4, 1946 in New York, New York but moved to Miami, Florida shortly thereafter. He attended Coral Gables High School and graduated from there in June, 1963. He received the degree of Bachelor of Arts from the University of Miami in June, 1967.

Enrolling in the Graduate School of the University of Florida in September, 1967, Mr. Jacobson was a Graduate Teaching Assistant from September, 1967 to June, 1972 in the areas of both general and organic chemistry while pursuing his work toward the degree of Doctor of Philosophy.

Harvey Lewis Jacobson is married to the former Cynthia Bridge. He is a member of the American Chemical Society and Alpha Chi Sigma chemistry fraternity.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

John A. Zoltewicz, Chairman
Professor of Chemistry

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Merle A. Battiste
Professor of Chemistry

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I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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Associate Professor of Biochemistry

This dissertation was submitted to the Department of Chemistry in the College of Arts and Sciences and to the Graduate Council, and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

August, 1973

Dean, Graduate School